Medical Science

25(118), December, 2021

A malignant transformation of benign phyllode tumor of breast and its management: A case report from India

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To Cite:
Rajput M, Akhter MJ, Lamture YR, Jagtap G. A malignant transformation of benign phyllode tumor of breast and its management: A case report from India. Medical Science, 2021, 25(118), 3231-3236

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Peer-Review History
Received: 02 November 2021
Reviewed & Revised: 03/November/2021 to 28/November/2021
Accepted: 29 November 2021
Published: December 2021

Peer-review Method
External peer-review was done through double-blind method.

ABSTRACT

Phyllode tumor (PT) of a breast is mostly benign, it shows a very rare transformation into malignant PT. Globally, less than a percentage of cases get reported for breast tumors. We reported the case of a recurring tumor in a woman of age 48 years with a lump on her left breast. She has gone through a resection twice. Firstly, post excision H/P reported fibroadenoma. Secondly, the excision of benign PT transformed to malignant phyllode within 3 months of resection. The results from images of CT scan, intraoperative, and pathological slides from the specimen of mastectomy have made us conclude that the malignant transition is caused by a mutation in residual tumor cells. Then, the total mastectomy with low axillary lymphadenectomy was done. Further, the patient was advised for adjuvant chemotherapy within 2 weeks and radiation therapy to the chest within 4 months of surgery. The patient is also advised to attend the follow-up appointments with the oncologist monthly for a minimum of 2 years after completion of adjuvant chemo-radiotherapy.

Keywords: Breast, Benign phyllode tumor, Recurrence, Malignant transformation, malignant phyllode tumor.

1. INTRODUCTION

Phyllode tumors (PT) of the breast are one of the rare occurring tumors, incidence including one in out of every 100,000 women and accounting for only 0.5 percent of all breast cancers (Testori et al., 2015). Women between the ages of 35 and 55 are more vulnerable to develop the tumor (Testori et al., 2015). Breast fibroepithelial tumors, such as fibroadenoma and phyllode tumors, are biphasic neoplasm. Core needle biopsy differentiates phyllodes from fibroadenoma, but in doubtful cases excision biopsy is helpful. The transformation of phyllodes tumor to malignant PT is an uncommon event, accounting for only 5-10% of all phyllode tumors (Wolbert et al., 2018). It is an aggressive tumor that spreads through the hematogenous route, primarily to the lungs, pleura, and bones. In, merely 20% of phyllode tumor cases, the

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profound axillary lymph nodes are involved, among which only <5% getidentified as positive nodes in the clinic (Kim et al., 2019).

Surgery is the first choice of treatment for confirmed cases of phyllodes tumor, followed by adjuvant therapy in combination with radiation therapy. The excision of phyllodes tumor with adequate margin is the advisable treatment according to the NCCN guidelines. One study has reported, that around 18.9% of the patients with a history of phyllode tumor again develop a recurrent borderline or malignant tumor (Kim et al., 2019). Also, the tumor reoccurs within two years of initial excision, in case of inadequate margin (Pornchai et al., 2018). The malignant transformation of phyllodes tumor from benign phyllode tumor is one of the rarest and infrequent forms of breast cancer (Pornchai et al., 2018). The malignant PT mainly gives a poor prognosis. There is a limited case report of the alteration of benign PT to malignant PT. Here, we report the case of a benign PT that transformed into a malignant PT within a short time interval of recurrence at the same location, also exhibiting the management of the malignancy.

2. CASE PRESENTATION

A female 48-year of age has presented to asecondary carehospital at Dongargaon in Chhattisgarhin January 2019, with a lump on the left breast of 2-cm in size at the upper-inner quadrant. An excision biopsy is done by radial incision. Histo-pathology (H/P) report ofthe excised specimen is fibroadenoma as per documentation in her hospital discharge card. Again she presented with a recurrent lump of size 4cm at the site of the scar after 2 years to the same hospital.An excision biopsy was done by horizontal incision. The H/P report showed a benign phyllodes tumor (Fig-1).

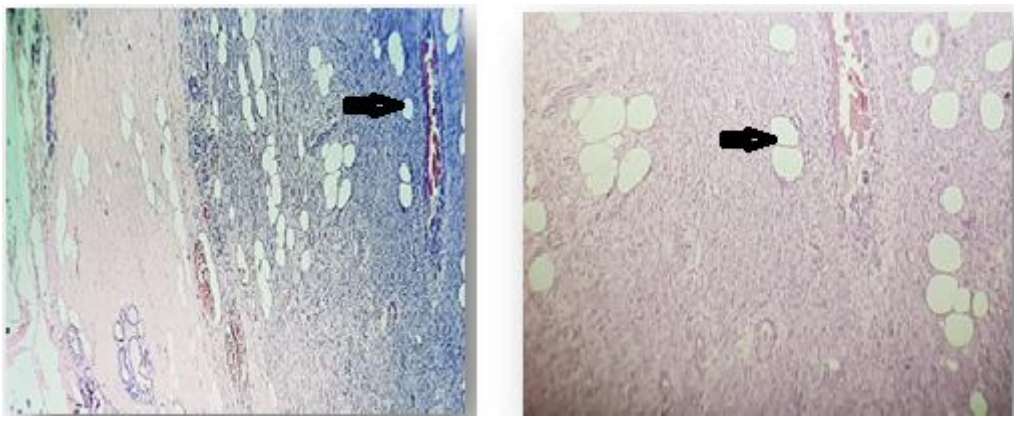

Figure 1 The H & E stained slides of benign phyllode tumor. **1a.** 10X magnification and **1b.** 40X shows well-demarcated pushing margins with cellular fibrocollageneous stroma with arrow depicting stromal spindle cells with minimal mitosis arid pleomorphism, whereas ductal and glandular elements appear to be unremarkable (see arrow).

Again in May 2021, she visited a tertiary care hospital in Junwani, Durg, Shri ShankaraCharya. Later, the case was presented in the Institute of Medical Sciences, Durgdistrict, Chhattisgarh. The case represents a rapidly expanding mass beneath the site of previous scar marks. The female had no family history of breast cancer. Moreover, she had menarche at 12 years of age and menopause at the age of 45 years. She had 3 pregnancies (gravida) and 2 live births (para). On the examination of the breast, there is a small area of redness surrounding previous scar marks. Leading to the finding of a firm lump of 7-cm which is fixed to underlying muscles at the 11 o'clock position of the left breast (Fig-2). It was fixed only to previous scars of skin; the nipple-areola complex was normal. There were few palpable lymph nodes on the ipsilateral axial, largest measuring 2cm of a central group of the lymph node. The contralateral breast was normal. Biochemical examination revealed no significant abnormalities. The preoperative CT scan showed a large well defined, lobulated, iso-dense mass at the upper inward quadrant of the left breast opposite to 1st& 2nd rib (Fig-3). The fat planes between the lesion and the left pectoralis muscle appear to be lost. The lesion measures 7 × 6 cm. with associated retraction of overlying skin. No evidence of calcification was noted in the lesion. There are limited lymph nodes noted in the B/L axilla, the largest measuring 1.8×1.6 cm in the left axilla without any evidence of distant metastasis to the chest. Visualized skeleton appeared normal. As the patient reacted to contrast, we did not allow for a contrast CT Scan for the same pathology.

On reviewing the previous block & slide specimen of 2019 by a senior pathologist. The microscopic findings disclosed an expanding stromal growth with the fibroepithelial lesion. Also, the normal mammary lobule and adipocytes are seen to be entrapped with multifocal infiltration. In the stroma, there were moderate hypercellularity and nuclear atypia were observed. Though, there was no confirmation of stromal overgrowth. The small tumor buds protrudinginto the margin of the surrounding

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tissue were seen. The Mitotic count was 2/10 high power field (HPF). The final report of Hematoxylin & Eosin (H & E) stain concluded the finding of benign phyllodes tumor.

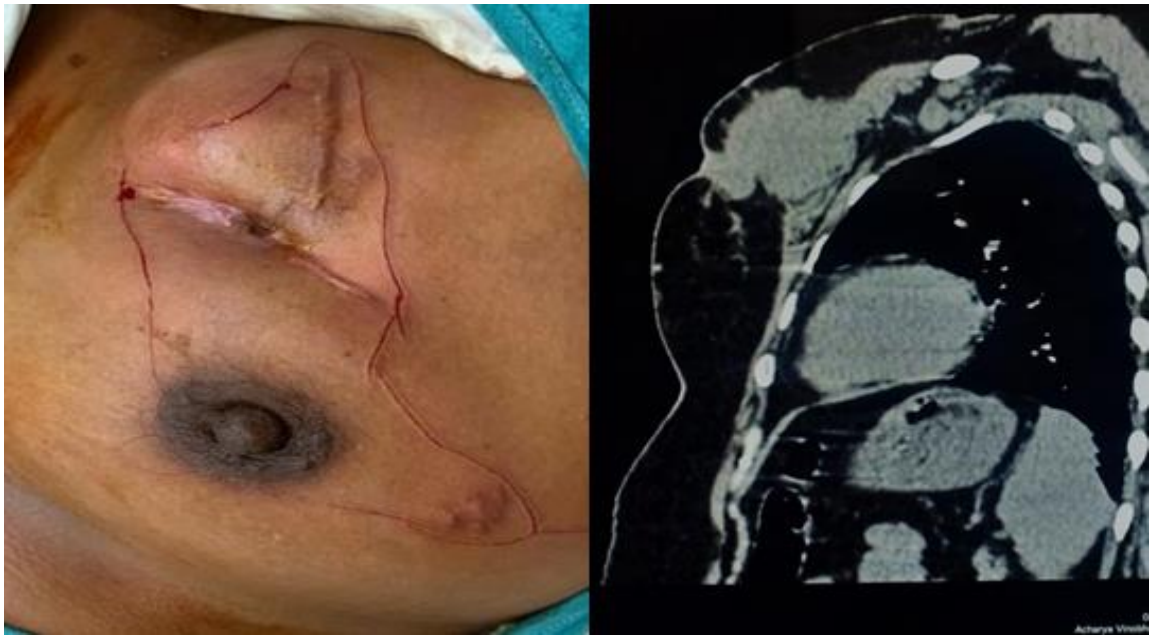

Figure 2a. The picture of resected breast depicting the underlying lump of 7cm at 11 o'clock position; **2b**. The CT scan shows the large lobulated mass.

3. RESULT

Considering the size, rapidity of growth & palpable LN, the patient endured a total mastectomy, including excision of low axillary nodes with the thickness of 1 cm of pectoralis major at the site of loss of fat planes (Fig. 3). Then, the wound is saline washed, keeping 16-no. suction drain and sealed with 2-0 vicryl stitches. The procedure was dull, the drain is been removed on the 4thday, and the patient was discharged on the 10thpostoperative day. Pathology examination by the same senior consultant showed a large diameter of 7-cm size phyllodes tumor, showing invasiveness in the pectoralis major muscle without margins, varying in size from 2 mm to 20 mm. The H&E tumor slide revealed moderate to marked hypercellularity of stroma and stromal atypia, with a focal vague border. Moreover, sufficient stromal overgrowth is seen with a mitotic count of 5/10 HPF (Fig. 4) and Lymph node double-positive (LN++). Further, the Immunohistochemistry (IHC) stained slides for Ki-67 showed strong nuclear positivity (Fig- 5a), and stain for SMA, CD10 showed strong cytoplasmic positivity (Fig 5b & 5c). Hence, the pathological report findings showed malignant phyllodes tumor with Ki-67 nuclear positivity and SMA, CD10 cytoplasmic positive.

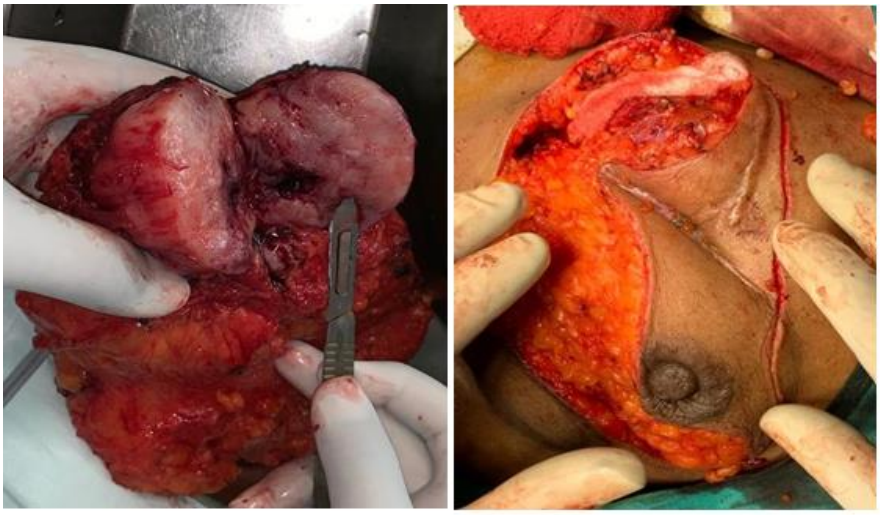

Figure 3 Total mastectomy of patient revealing phyllodes tumor.

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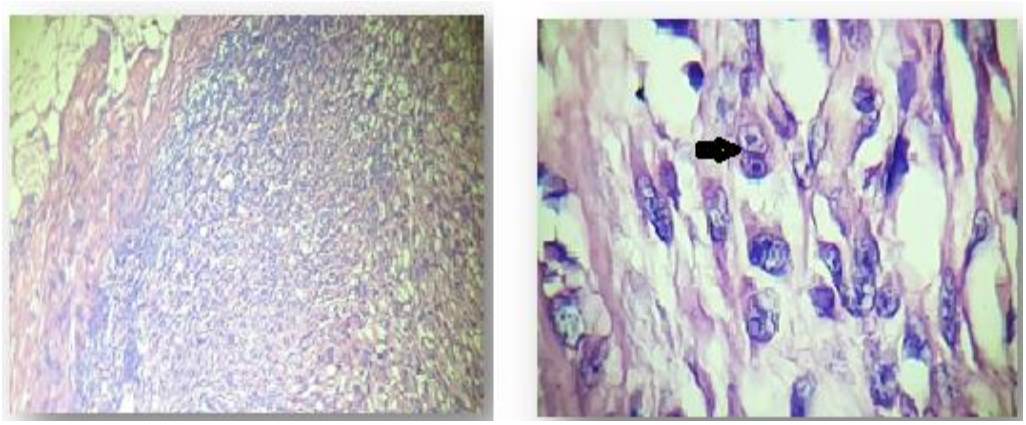

Figure 4 H&E slide of malignant phyllodes tumor; **4a**. 10x magnification and **4b.** 40x magnification show infiltrative tumor edges. Stroma appears to show hypercellular fibrocollagenous stroma. Spindle cells of stroma show increased cellular pleomorphism of more than 10/10 HPF miotic activity (see arrow).

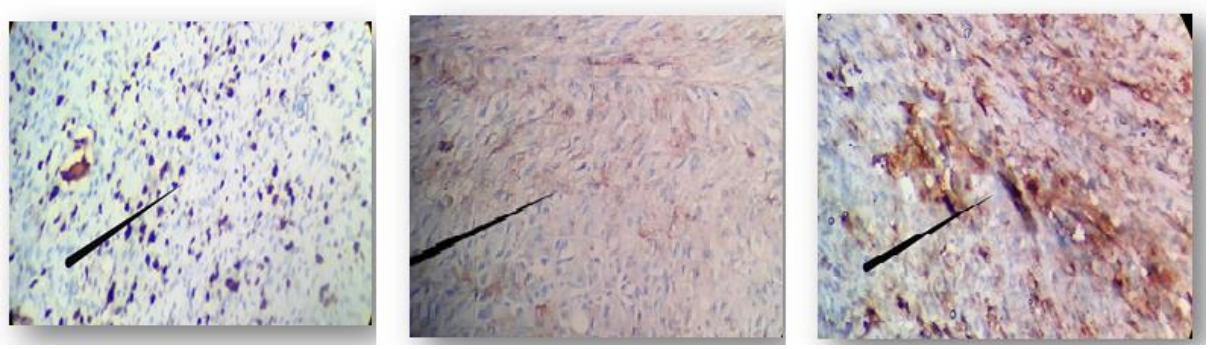

Figure 5 Immunohistochemistry (IHC) stained slides showing; **5a.** Ki-67 strong nuclear positivity **5b.** SMA positive.**5c.**CD 10 positive.

The Lab findings from our study revealed the molecular marker CD34=negative, CD117=negative, and in approximately, 80% p53 stained moderate-to-strong. The Ki67=7%, 60% staining of moderate membranous for EGFR, β-catenin gave no nuclear staining. Also, Bcl2 and ER are negative. Hence, our findings revealed the feature of primary tumor which included undifferentiated border, moderate stromal hypercellularity, and stromal atypia, certainly not stromal overgrowth and a count of mitotic 2/10 HPF; therefore, supporting the outcomes of benign to borderline phyllodes tumors. Moreover, in support of confirmation of malignant phyllodes, our findings revealed recurrent tumors including focally undifferentiated border, moderate to marked stromal hypercellularity, and stroma atypia, with noticeable stromal overgrowth and a count of mitotic 10/10 HPF.

The patient case has been reviewed with the medical and radiation oncology team, at the multidisciplinary tumor board and the decision is made to proceed with adjuvant chemotherapy and radiation therapy. Although, the examination and lab reports showed there is no involvement of lymph node and no malignant cells in the margin, including the nearest distance to the margin to be 2mm requires additional radiation therapy. The patient was advised to be in touch with consulting oncologist for a minimum of 2-years to followup the regular monitoring of clinical and imaging results.

4. DISCUSSION

In terms of treatment, distinguishing between afibroadenoma and phyllodes tumor in middle-aged women is essential. The phyllodes tumor is not well differentiated from fibroadenoma as it represents a clinical similarity including round lobules, mobile and painless mass similar to a fibroadenoma. The imaging techniques and cytological examinations also do not reveal the differences. Therefore, the final diagnosis can be confirmed by histopathology & immunohistochemical analysis. Currently, few reports have suggested the use of MRI for diagnosis before operating (Jang et al., 2012). The clinical behavior of phyllodes tumors is irregular, sometimes representing benign phyllodes or as distant invader in borderline (Telli et al., 2007). Therefore, to prevent the phyllodes tumor to become large, malignant, and aggressive, it is highly important to identify it in the early stages.

According, to the National Comprehensive Cancer Network (NCCN) guidelines, the phyllodes tumor management should be according to the size of the tumor for say, the phyllodes tumor of more than 3.0-cm is to be surgically removed, also showing clean

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margins of more than equal to 1.0-cm without axillary staging, benign, borderline or malignant (Gradishar et al., 2017); in case of a more than 10 cm-sized phyllodes tumor, whether benign or malignant, mastectomy is advisable. The proper management of phyllodes tumors can increase the survivability rate in patients. Some studies have shown the increase in 5-year survival rates in malignant phyllodes tumors from 54% to 82% also, the 10-year survival rate from 23% to 42% (Verma et al., 2010). Also, to maintain the integrity and shape of the breast the lumpectomy is advisable over mastectomy. To opt for the lumpectomy, clinicians play a major role in diagnosing the tumor location and size, and area.

Formal axillary dissection could be unnecessary as Phyllodes Tumors has predominantly hematogenous metastases. In our case, the removal of low axillary lymph nodes is advisable, also those, it is suggested in patients with large breast mass or palpable lymphadenopathy (Parker and Harries 2001). For the local reappearance of PT after excision, the treatment is re-excision in case of asuitable margin of 1 cm and an adequate cosmetic outcome. Conversely, if the margin is inadequate and surgery is affecting the cosmetic outcome then mastectomy should be taken into consideration. In the case of younger ladies with Phyllodes tumor reconstruction of the breast can be done as an additional step with WLE or simple mastectomy. In our study, total mastectomy with low axillary node excision was done.

It's been also suggested that inadequate margin, could cause mutation and transformation of residue benign phyllodes tumor to malignant (Hajdu et al., 1976). Many studies have concluded the higher chances of recurrence in patients with margins less than 1.0cm, ranging from 16.7% to approx. 40% (Wolbert et al., 2018). The recurred tumor generally shows histological similarity with primary or main tumors, though they are more cellular, having a focal area of a typical cell (Hajdu et al., 1976). The phyllodes tumor should be properly managed by clinicians, so that not only could be properly managed if it reoccurs but also show sufficient atypia to give a sign of malignant PT significance (Hajdu et al., 1976). In our findings, the tumor recurrence gave the significance of increased mitotic count number, stoma overgrowth, Stromal atypia, and cellularity.

Till, today there is no proper advisable treatment such as systemic chemotherapy, radiotherapy, and hormonal therapy for malignant phyllodes tumors (Wolbert et al., 2018). Also, there are no shreds of evidence from double-blinded, multicenter studies (Wolbert et al., 2018). Though, in some cases, radiotherapy has been advised for indigenous control of the disease (Stockdale and Leader, 1987) including, in high-risk PT, also those measuring greater than 5cm in size, overgrown Stromal, showing more than 10 mitoses per HPF, or having positive margins. It is advisable to administrate radiation therapy within 4 months of surgery (Barrow et al., 1999). One of the studies from multi-institutional concluded that the local recurrence rate was low after adjuvant radiotherapy compared to patients with resection alone having a negative margin (Barth et al., 2009). It's been also found that patient has also get benefited from adjuvant chemotherapy, taken in combination of doxorubicin and dacarbazine, which showed benefits in patients having large or more than 5.0 cm of tumor size (Morales-Vásquez et al., 2007).

5. CONCLUSION

The case of phyllodes tumor recurrence is presented by us showing the ability to transform into malignant. The literature and data from our case study can be concluded that benign phyllodes tumors can transform to malignant phyllodes tumors, even after being locally resected as residual tumor cells carry a mutation for the transformation. Therefore, it is important to completely resect with adequate margin to reduce the risk of relapse and alteration into malignant PT. Hence, regular follow-up is recommended to the patient, a minimum of 2 years for the proper management of the condition.

Acknowledgement

We thank the participant who contributed in the study.

Author Contributions

All authors contributed equally to the case report.

Informed Consent

Written & Oral informed consent was obtained from patient.

Funding

This study has not received any external funding.

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Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are presented in the paper.

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