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Case Report

Malignant Phyllodes: Report of Three Cases and Review of the Literature

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Abstract

Phyllodes tumors (PT) accounts for up to 1% of all breast tumors. Although it is considered to be a rare tumor which is mostly benign. Some of the Phyllodes tumors could be malignant, which are characterized by aggressiveness in biological behavior with the chance of local recurrence or metastasis. In this presentation, we report three cases of large malignant PT.

Keywords: Phyllodes; Breast; Fibroepithelial Tumors.

Introduction

Phyllodes tumors (PT) previously known as Cystsarcoma Phyllodes are rare tumors that arise from the connective tissue and periductal stroma of the breast sparing the ducts and the glands. Thus, it is categorized as fibroepithelial tumors of the breast accounting for 0.3% to 1% of all breast tumors [1,2]. The World Health Organization in 2003 has classified Phyllodes tumors into three mains categories based on their histological features, benign, borderline, or malignant [3]. Phyllodes tumors are commonly benign (35% to 64%) with documented malignancy ranging between 10% - 30% [4].

The clinical features of PT carry resemblance to fibroadenomas with variable sizes. However, it has the tendency of rapid growth, multiplicity, active biological behavior, local recurrence, or distal metastasis [5]. The challenge is to achieve accurate diagnosis and be able to perform surgical excision with safety margins. Hereby, we report three cases of Asian women presenting with extreme sizes of PT.

Case presentation

Case 1

40 years old Pilipino a mother of 2 children who lost follow-up after wide local excision with safe margins of borderline PT in 2018. She presented at this time to the Breast Clinic with a left breast mass of 3 months duration. There was a progressive increase in size associated with pain, skin redness, and a foul-smelling bloody nibble discharge. No other associated symptoms. Menarche at 16 years, strong positive family history of breast cancer was documented.

Local examination revealed marked asymmetry, enlarged left breast with overlying stretched skin, erythema, and peau d'orange with distortion of nipple and areola complex with ulceration. On palpation confirmed the presence of the mass occupying the center of the left breast, hard in consistency measuring 10x10 cm. with no palpable axillary nodes. (Figure 1a)

Ultrasound demonstrated a large lobulated hypoechoic mass with an angular margin occupying nearly all the breast extending to the nipple, associated with overlying skin thickening and nipple

distortion. Multiple axillary lymph nodes with diffused cortical thickening, measuring 13.1x8.7mm, same findings were confirmed by mammogram and was reported BI-RADS 5. (Figure.1b)

Metastatic workup utilizing CT-CAP scan (for chest, abdomen, and pelvis) and the Bone scan was reported as negative. Ultrasound-guided core biopsy of the left breast mass and left axillary lymph node (LN) reported malignant PT of left breast mass and reactive axillary lymphoid tissue.

Mastectomy was the consensus by the Multidisciplinary team (MDT) meeting. The patient underwent left mastectomy and axillary sampling of the enlarged lymph nodes. Breast tissue measured around 26x26 cm and weighed 3.5 kg (Figure 1c)

Immunohistochemical stains showed, Pan-CK highlight limited epithelial elements and marked stromal expansion, Ki-67: 30-40%, ER: positive, CK5/6: weak, P63: highlight myoepithelial cells, Calponin: highlight the myoepithelial cells (Figure 2) The diagnosis was reported as Malignant PT with uninvolved axillary nodes.

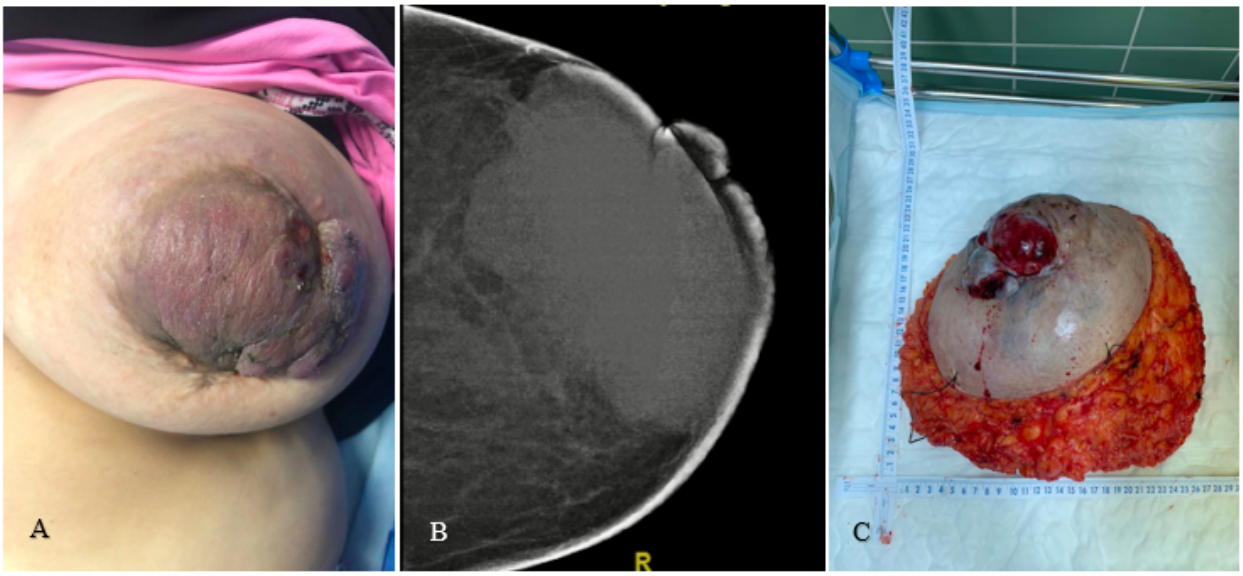

Figure 1: A. Enlarged breast mass showing stretched erythematous skin with distortion of the nipple areola complex B. Mammogram Craniocaudal view demonstrating a large mass with skin thickening and nipple infiltration C. Demonstrating the mastectomy.

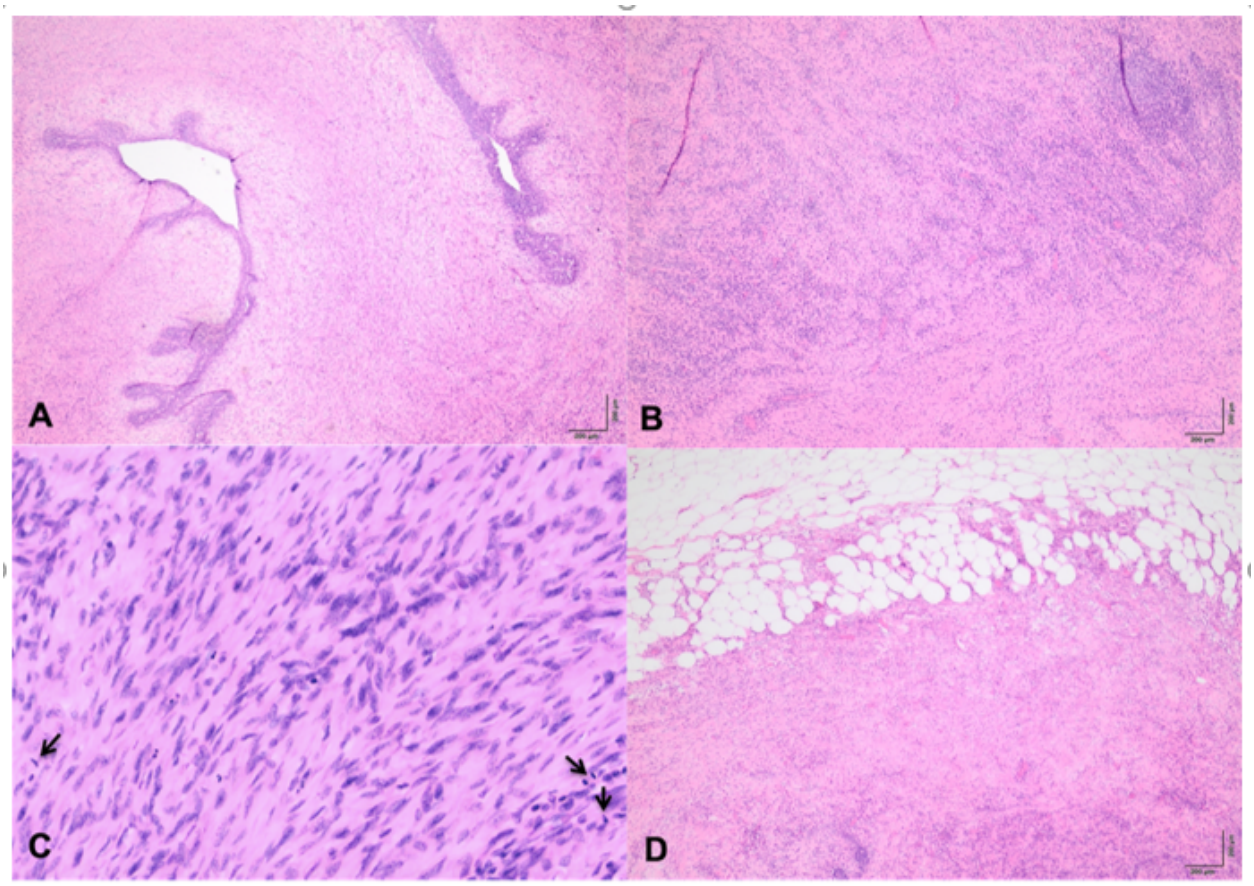

Figure 2: A. Section of the lesion shows leaf-like epithelial pattern with sub-epithelial condensation of stromal cells. (H & E, 4x magnification) B. Marked stromal overgrowth displaces the epithelial structures in Malignant Phyllodes Tumor. (H & E, 4x magnification) C. Frequent mitotic figures are noted in the stroma (Arrows). (H & E, 40x magnification) D. Diffuse infiltration of the tumor cells into the surrounding adipose tissue. (H & E, 4x magnification).

Case 2

This is a 59-year- old single Indonesian female noticed 2 years prior to her presentation, it started as a stable painless mass until 4 months prior to presentation as she noticed a rapid increase in size fungating through the skin, associated with skin erythema and yellowish discharge. Negative history of Breast Cancer.

Local examination showed breast had a fungating growth on the left upper breast with palpable left breast mass occupying almost the entire breast (Figure 3a). The remaining examination was unremarkable.

Ultrasound and mammography demonstrated a large ill-defined heterogeneous dense mass with multiple internal coarse calcifications and surrounding architectural distortion and parenchymal edema occupying the whole left breast, measuring approximately 15.0 x 12.6 x 14.0 cm. protruding anteriorly with overlying skin thickening, posteriorly abutting the pectoralis muscle, with a few prominent axillary prominent nodes with diffuse cortical thickening is noted (Figure 3b). Reported as BI-RADS. Metastatic workup was reported as negative.

Core biopsy of the left breast showed atypical spindle cell lesion with the immunohistochemical stains: P63: Focally positive, CD34: Focally positive, CK 5/6: Negative, CK 8/18: Negative, SMA: Negative, S100: Negative, B- catenin: Negative. With a correlating differential diagnosis of spindle cell carcinoma, phyllodes tumor, and primary or metastatic sarcoma. (Figure 4)

The patient underwent left mastectomy and axillary node sampling based on the MDT meeting consensus. The Final Diagnosis was malignant PT With the presence of 15 Mitosis/ mm^2 with negative axillary nodes. Due to the size and extent of the disease, adjuvant external beam radiotherapy is suggested.

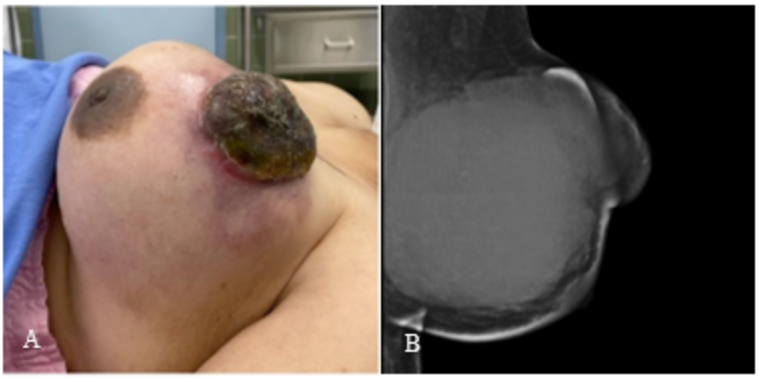

Figure 3: A. Enlarged Breast with supra areolar Fungating mass B. Mammogram demonstrating a large mass occupying the whole breast with skin infiltration and thickening in addition to abutting on the chest wall.

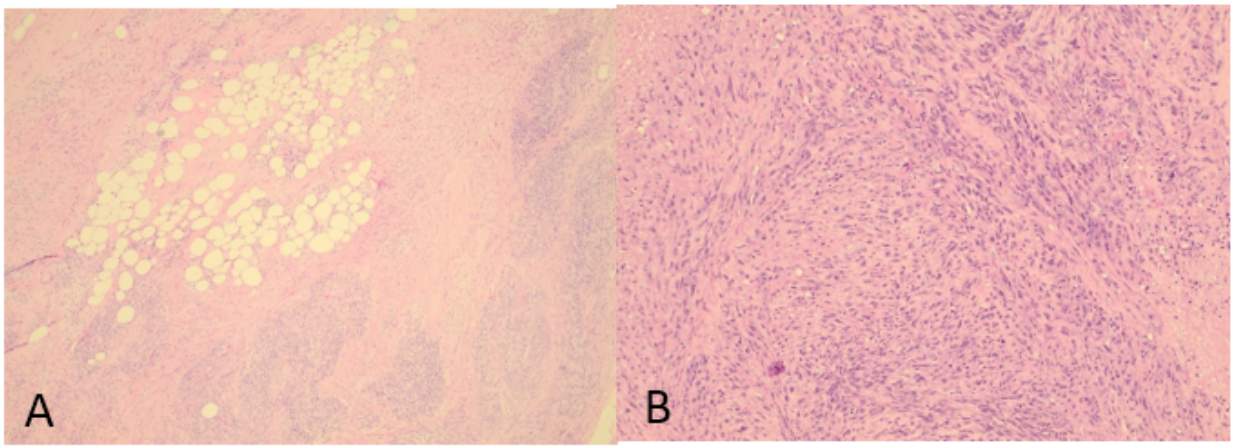

Figure 4: A. On low power magnification, stromal overgrowth is noted with presence of malignant heterologous elements (Lipogenic) in Malignant Phyllodes Tumor (H&E, 10x magnification). B. The tumor cells show marked hypercellularity, atypia, frequent mitoses and necrosis [top left corner and bottom right corner] (H&E, 20x magnification).

Case 3

28-year-old Afghani mother of a one-child presented to the breast clinic complaining of a right breast mass of 2 years duration with progressive increase of size and heaviness. It progressed to triple the size of the contralateral breast associated with nipple retraction. No axillary pain or masses. Negative history of breast cancer. Menarche started at age of 17.

Local examination revealed a large multinodular mass that occupy the whole right breast stretching skin down to the abdomen with erythema and multiple small ulcerations on the lateral side. The right nipple is retracted with no discharge. On palpation, multiple lobulated large masses, firm with stretched overlying warm and tender skins. Contralateral breasts and axillae were unremarkable. (Figure 5)

US and mammogram showed an out-of-range large heterogenous lobulated mass noted occupying the whole right breast estimated measurement is around 22.1 x 18.3 x 22.1 cm with multiple internal cystic apace and central necrosis as well as internal vascularity. Noted, prominent right axillary lymph node measuring 11.3 x 5.0 mm with a cortical thickness of 3.1 mm. The final assessment was BI-RADS 4C, with High suspicion of malignancy.

Core Biopsy was nonconclusive showing a Fibroepithelial lesion with focal coagulative necrosis and no evidence of

malignancy. Considering the size of the breast and multiple large disfiguring masses, a mastectomy was performed with excised breast weighing 4.5 kg. (Figure 6). The Final histopathological report showed malignant phyllode tumor that measured 21*20*16 cm. and all the margins were negative for malignancy (Figure 7).

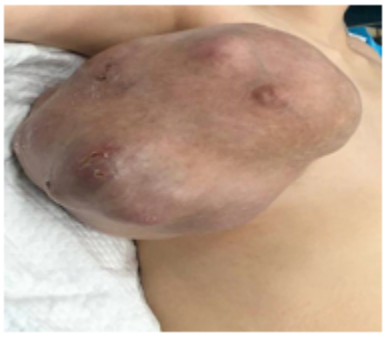

Figure 5: Demonstrating the totally replaced breast with large lobulated masses.

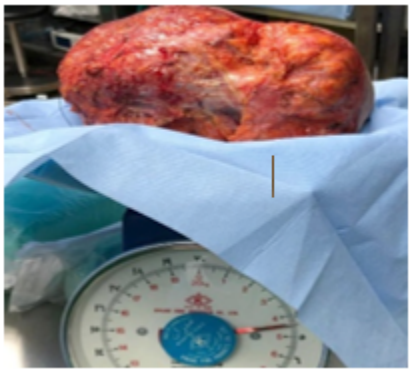

Figure 6: Demonstrates the weight of the mastectomy specimen of 4.5 Kg.

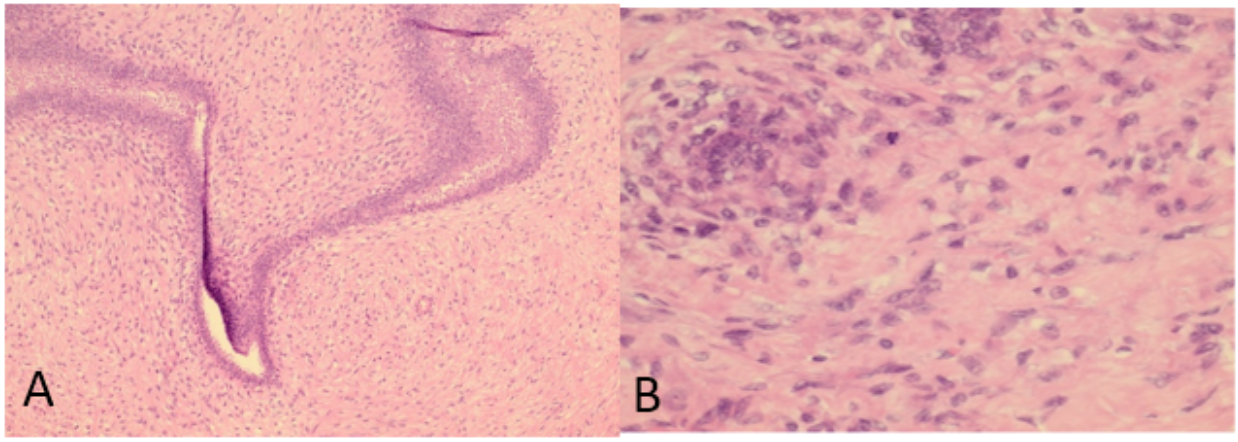

Figure 7: A. Marked stromal cellularity and cytological atypia are noted in Malignant Phyllodes Tumor (H&E, 10x magnification). B. Numerous mitotic figures are noticed in the stroma (H&E, 40x magnification).

Discussion

Phyllodes tumors (PT), also known as cystosarcoma phyllodes are unusual breast tumors originating from fibroepithelial components. Throughout the years, the reported incidence of PT in all its forms remains to be <1%, with a mean age of occurrence ranging from 35-55 [1,2]. These tumors are more common to occur in women than men, with reported a correlation between multiparity and the incidence of PT [6,7], yet there are also reported cases in pediatric patients [8,9].

The World Health Organization classified PT into benign, malignant, and borderline tumors based on histopathologic features, including the degree of stromal atypia, number of mitoses, stromal overgrowth, nuclear uniformity, and the tumor margins/ border infiltration [3,4] and among the three subtypes, malignant PT is the rarest entity which accounts for approximately 10% to 30% of all PT [4].

Clinically benign PT resemble fibroadenomas in which they are usually well-circumscribed, painless with size averaging around 5cm, but they are characterized by aggressiveness in biological behavior as they can grow into large sizes, and can also ulcerate and bleed with a chance of local recurrence or metastasis [10,5]; this chance of recurrence could occur post excision, independent of it being of benign or malignant pathology [11]. These tumors tend to grow faster since they have higher stromal cellularity compared to fibroadenoma lesions [5,12]. Moreover, core biopsy results for both PT and cellular fibroadenoma may mimic each other. Cystic spaces are seen in histological examination and leaf-like appearances by gross examination [10,12]

Histological diagnosis of PT is made when the fibroepithelial architecture expresses an exaggerated intracanalicular pattern with leaf-like fronds protruding into dilated cystic spaces accompanied by stromal hypocellularity. Benign PT are well circumscribed with pushing tumor margins, minimal stromal overgrowth, cellularity and atypia, and mitoses of ≤4 per 10 high-power fields (HPFS). The main histological clue to distinguish between fibroadenoma and benign PT is the presence of increased stromal cellularity in PT [5]. On the other hand, Malignant PT have higher stromal hypercellularity and cellular pleomorphism, ≥10 mitosis per 10 high HPFS, stromal overgrowth, and infiltrative margins [12].

The clinical presentation of PT is usually with a rapidly growing mass, involving a quarter to a half of the breast tissue, which is mobile with clearly identified borders. It also presents with tense overlying skin and dilated veins. Axillary lymph node enlargement could also occur with PT [13,14]. Due to the usually large size of PT, skin ulceration could occur; yet it does not pertain to being a sign of malignancy [13]. The same goes for axillary lymph node enlargement, which occurs due to the presence of infections and necrosis accompanying the mass [6].

In general, the presence of intralesional clefts and cystic spaces on ultrasound may support the diagnosis of PT. Malignant PT appears to be a smooth, poly-lobulated mass in ultrasonography. Also, it looks like fibroadenoma with well-circumscribed hypoechoic mass to a heterogenous mass, but with features suggestive of malignancy such as ill-defined margins, microcalcification or lobulation [12]. On mammography, PT can appear as an oval or round mass with either well- or ill-defined margins, which is not specific to rule out other neoplasms. In some cases, mammography of malignant type showed round or oval with lobulated margins with higher density than the surrounding parenchyma. [15] Tan, et. al. compared the genetic mutations found between the three variants of PT, and they found that the borderline and malignant variants harbored additional mutations in the cancer driver genes. [16] Whereas Lae, et. al. found that the average mutations found in borderline and malignant PTs were 6 in comparison to 1 mutation in benign PTs [17].

Magnetic resonance imaging (MRI) is a useful diagnostic tool which helps in diagnosing malignant PT in a very dense breast with a difficult mass, or when mammography and sonography could not give an accurate diagnosis. On MRI, appearance of heterogeneous inner structure, non-enhancing septations, and slit-like patterns can indicate a diagnosis of PT [12,15]. Further investigations such as True-cut biopsy is essential for diagnosis as histological assessment and grading of PT can be made [15].

Metastases of PT occur in malignant types and occur via infiltration of adjacent structures or in a hematogenous manner, and could rarely occur through lymphogenic metastasis [18,19].

Surgical excision remains the gold standard method of treatment of PT, no matter the surgical technique used to achieve it [20]. A clear surgical margin of 1-2 cm is required to prevent local recurrence [21]. And studies have shown that there isn't a difference in the risk of recurrence between different methods used in excision (lumpectomy, wide local excision, simple mastectomy, or modified/radical mastectomy) when a good surgical margin is achieved. And that the only predictor of risk for recurrence is the size of the tumor and a malignant pathology [2,22].

A multivariate analysis conducted by Spitaleri, et al. on 172 patients with phyllodes tumors showed that a positive margin (despite lack of its definition) is associated with a fourfold higher risk of local or distant disease [23]. Moreover, a clear surgical margin is more important in malignant phyllodes tumors as a recent meta-analysis included 9234 patients with positive margins, and concluded that the risk of local recurrence was significantly increased in the malignant type [23]. Axillary dissection is not required as the involvement of lymph nodes in phyllodes tumor are rare [23], but axillary lymph node sampling can be done in patients where suspicious lymph nodes were detected during evaluation [6].

In cases diagnosed as malignant PT, surgical excision remains the mainstay of treatment, where chemotherapy, hormonal manipulation and radiotherapy are used yet have not shown any significant effect on decreasing mortality or increasing life expectancy [19,24]. Adjunct radiotherapy can have an effect on the local recurrence rates in borderline and malignant types with 10-year local control rates (86% with radiation versus 59% without radiation), but does not play a role in the disease-free or overall survival rate [4,5,12,23].

It showed that the prevalence of local recurrence if tumor size greater than >10 cm is reached up to four times if the surgical margin was less than 1 cm, the risk of local recurrence increased by five-fold and the stromal overgrowth can increase the local recurrence rate by seven-fold [10]. Thus, Radiotherapy can be considered in phyllodes tumors greater than 5 cm, with more than 10 mitoses per high power field, with stromal overgrowth, or with positive margins. [5].

In a study done by Mitus, et al., adjunct radiotherapy was given to patients with malignant phyllodes tumors whose tumor-free margins were <10 mm, it showed that the 5-year disease-free survival rates were identical with patients whose margins were wide (≥10 mm) and did not receive radiation. [12].

The prognosis in patients of benign PT is favorable and shows a good long-term disease-specific survival and is reported to be 80-90% in patients who had the malignant subtype or malignant degeneration [2,25]. On the other hand, in malignant cases with hematogenous metastasis, the prognosis drops and so does the life expectancy. [19] Metastasis of phyllodes tumors was reported in 13-40%, and they commonly metastasize to the lungs and soft tissue sarcoma. once lung metastases are detected, resection is preferred. In the case of soft tissue metastasis, the chemotherapy regimen will be decided based on the treatment guidelines for soft tissue sarcoma [23].

In conclusion, PT diagnosis and management can be challenging. Surgical excision with negative margins remains the ultimate goal for preventing recurrence.

Declarations

Ethical Approval: Not applicable.

Competing interests: No conflicts of interest in this work.

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