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BEYOND THE LEAF-LIKE PATTERN: MALIGNANT PHYLLODES TUMORS WITH HETEROLOGOUS DIFFERENTIATION: A CASE SERIES

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ABSTRACT:

Background: Malignant Phyllodes Tumors (MPTs) are rare fibroepithelial breast neoplasms, accounting for 8–20% of all Phyllodes tumors. When heterologous differentiation—such as liposarcoma, fibrosarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, or rhabdomyosarcoma —is present, these neoplasms exhibit unique histopathology and clinical characteristics, though available data on this phenomenon remains limited due to its rarity.

Case presentation: Three female patients aged 48 to 64 presented with progressively enlarging, painless breast lumps ranging from 4.8 to 6.4 cm. Tumors were located in different breast quadrants. Histopathological examination confirmed malignant Phyllodes tumors with rare heterologous sarcomatous differentiation—chondrosarcoma in Case 1, angiosarcoma in Case 2, and combined osteosarcoma with chondrosarcoma in Case 3. All underwent modified radical mastectomy; and axillary lymph node dissection (ALND) was performed in one case. No recurrence was noted in Cases 1 and 2 at 18 and 6 months, respectively. No adjuvant therapy was given.

Discussion: MPTs with heterologous sarcomatous elements remain an exceptionally rare subgroup, posing significant diagnostic ambiguity. Thorough histologic sampling and immunohistochemistry are essential to differentiate these from metaplastic carcinoma or primary breast sarcomas. Prognostic indicators and treatment protocols for these variants are not well established due to their rarity. Current practice supports wide surgical excision with negative margins; adjuvant therapy decisions should be individualized, and close surveillance is advisable given the potential for aggressive behavior.

Conclusion: The case series highlight the exceptionally rare presentation of malignant Phyllodes tumours with heterologous sarcomatous differentiation. Detailed case documentation and long-term

follow-up are essential to better characterize their clinical trajectory and inform optimal management strategies.

Key words: Heterologous, Malignant, Phyllodes, Sarcoma.

Introduction

Malignant Phyllodes tumors (MPTs) are rare fibroepithelial breast neoplasms, accounting for less than 1% of all breast tumors [1, 2]. A distinct and aggressive subset of these tumors demonstrates heterologous differentiation, in which the malignant stromal component differentiates into non-native mesenchymal tissues such as osteosarcoma, chondrosarcoma, liposarcoma, rhabdomyosarcoma, or angiosarcoma [1, 3]. These tumors are challenging to diagnose and manage due to their rarity and histological overlap with other primary sarcomas or metaplastic carcinomas [4, 5].

Patients typically present with a rapidly growing breast mass, often exceeding 10 cm in size [2, 6]. Imaging usually reveals a circumscribed, heterogeneous lesion with internal necrosis or cystic changes. Core needle biopsy frequently fails to reveal the full extent of stromal atypia or heterologous elements, leading to diagnostic underestimation [3, 5].

Histologically, MPTs with heterologous differentiation show high stromal cellularity, marked nuclear pleomorphism, infiltrative margins, and frequent mitoses (>10/10 HPF) [6]. The presence of specialized components such as osteoid in osteosarcomatous areas or lipoblasts in liposarcomatous areas confirms heterologous differentiation [6, 7].

Surgical excision with wide negative margins remains the primary treatment. Due to the size and aggressiveness of these tumors, mastectomy may be necessary in many cases [9]. Local recurrence occurs in up to 40% of cases, particularly when excision margins are narrow or positive [9, 10]. While the role of adjuvant radiotherapy or chemotherapy is not well established, it may be considered in selected high-risk or recurrent cases [10, 11].

Prognostically, the presence of heterologous elements correlates with a more aggressive clinical course. Osteosarcomatous differentiation, in particular, is associated with early metastasis and poor outcomes [12]. Unlike typical breast carcinomas, these tumors spread hematogenously, with lungs, bones, and liver being the most common metastatic sites [11, 13]. Lymph node involvement is rare, and routine axillary dissection is generally not indicated [12].

This case series highlights the rarity and heterogeneity of these tumors and multidisciplinary approach involving pathologists, surgeons, and oncologists is essential. Early and accurate diagnosis, complete excision, and vigilant follow-up are crucial to improving patient outcomes.

Materials and Methods

This retrospective case series was conducted in the Department of Pathology at Belagavi institute of medical sciences evaluating cases of malignant phyllodes tumors with heterologous differentiation diagnosed between January 2018 and December 2024. Clinical data and pathology archives after obtaining appropriate institutional review board (IRB) approval.

Inclusion criteria comprised all cases of histologically confirmed malignant phyllodes tumors exhibiting heterologous stromal differentiation. Cases lacking complete histopathological documentation or follow-up data were excluded.

Tissue samples were fixed in 10% neutral buffered formalin and processed routinely. Hematoxylin and eosin (H&E)-stained slides were reviewed to assess stromal cellularity, atypia, mitotic count, stromal overgrowth, and the presence of heterologous elements.

Clinical parameters such as age, tumor size, and type of surgical intervention, adjuvant therapy, clinical outcomes (recurrence or metastasis), gross findings, histopathological features,

immunohistochemical profiles, treatment details, and follow-up information were obtained from institutional medical records, surgical oncology departments or direct follow-up calls when necessary.

Case presentations:

Case 1:

A 64-year-old woman presented with a gradually enlarging, painless lump in the upper outer quadrant of her left breast, first noticed three months earlier. She had no significant family history of breast malignancy but reported a prior lumpectomy for a benign breast lesion 22 years ago. On clinical examination, a non-tender, well-circumscribed mass measuring approximately 5cm was palpable without skin changes or axillary lymphadenopathy.

Mammography and ultrasound revealed a 5.2 × 3.5 cm solid mass with lobulated margins and internal cystic components. A core needle biopsy suggested a biphasic neoplasm, consistent with a borderline phyllodes tumor. She underwent a modified radical mastectomy with axillary lymph node dissection.

Gross pathology demonstrated a lobulated mass with slit-like projections, cystic areas and foci of hard calcified areas noted (Fig 1). Microscopic examination revealed malignant phyllodes tumor composed of increased stromal cellularity, moderate atypia, and focal heterologous elements resembling chondrosarcoma (Fig 3a, 3b). The mitotic rate was increased (11/10 high-power field. The surgical margins are free of tumor deposit.

Her postoperative recovery was uneventful. She is under regular surveillance, and at 18 months of follow-up, she remains clinically asymptomatic with no evidence of recurrence

Case 2

A 59-year-old postmenopausal woman presented with a rapidly enlarging, painless mass in the upper inner quadrant of left breast, noted over a six-week period. No significant past or family history of breast cancer. Clinical examination revealed a firm, mobile mass measuring approximately 5 cm, with no overlying skin changes or axillary lymphadenopathy.

Imaging with mammography and ultrasound demonstrated a 6.4 × 4.3 cm well-defined, hypoechoic lesion with internal cystic spaces and prominent vascularity. A core needle biopsy indicated a malignant phyllodes tumor (PT). The patient proceeded with modified radical mastectomy. Gross examination of the excised specimen revealed a lobulated, fleshy mass with areas of hemorrhage and necrosis (Fig 2). Histopathological analysis confirmed a malignant PT with high stromal cellularity, marked pleomorphism, and a high mitotic index (12 mitoses/10 high-power field). Notably, the tumor exhibited heterologous angiosarcomatous differentiation, characterized by anastomosing vascular channels lined by pleomorphic, hyperchromatic endothelial cells with brisk mitotic activity (>13/10hpf), and focal necrosis (Fig 4). Her postoperative was uneventful. She is on regular six-monthly follow-up, and at 6 months post-surgery, she remains disease-free with no evidence of local or distant recurrence.

Case 3

A 48year-old perimenopausal woman presented with a progressively enlarging, painless mass in the lower outer quadrant of her right breast, first noticed two months prior. She had no past history of breast disease. Clinical examination revealed a firm, mobile mass measuring approximately 4.4 cm, without skin changes or axillary lymphadenopathy.

Ultrasound and mammography showed a 4.8 × 4.1 cm well-circumscribed, heterogeneous lesion with internal cystic spaces and coarse calcifications. Core needle biopsy was suggestive of a malignant phyllodes tumor (PT).The patient underwent right modified radical mastectomy.

Grossly, the tumor appeared infiltrating lobulated gritty calcified with foci of cystic change noted. Histopathology confirmed a malignant PT with high stromal cellularity, moderate-to-severe atypia,

and a mitotic rate of 11 per 10 high-power field. Focal areas of osteosarcomatous and tiny foci of chondrosarcomatous differentiation were identified (Fig 3c). The patient was lost for follow-up.

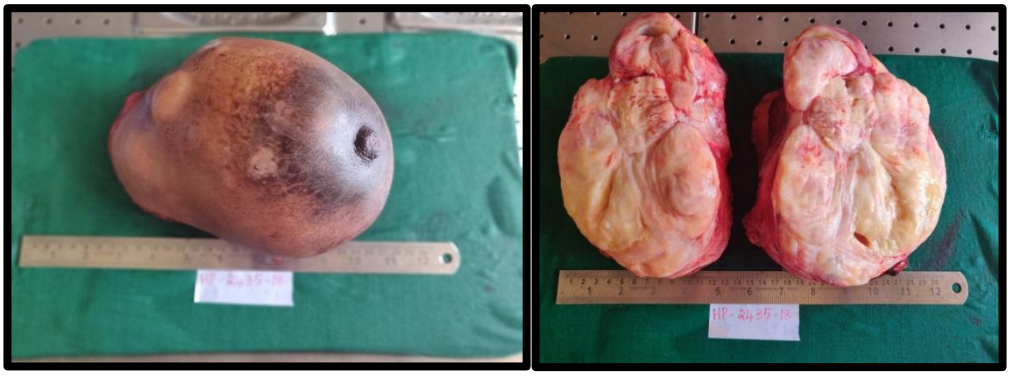

Figure 1: Gross photograph of malignant Phyllodes tumor a) Outer surface b) cut section

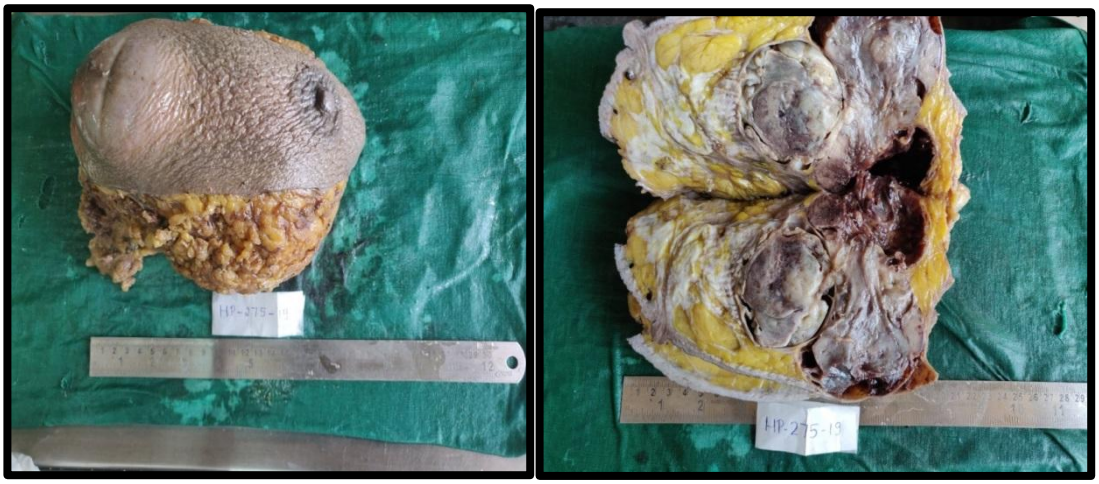

Figure 2: Gross photograph of malignant phyllodes tumor a) Outer surface b) cut section

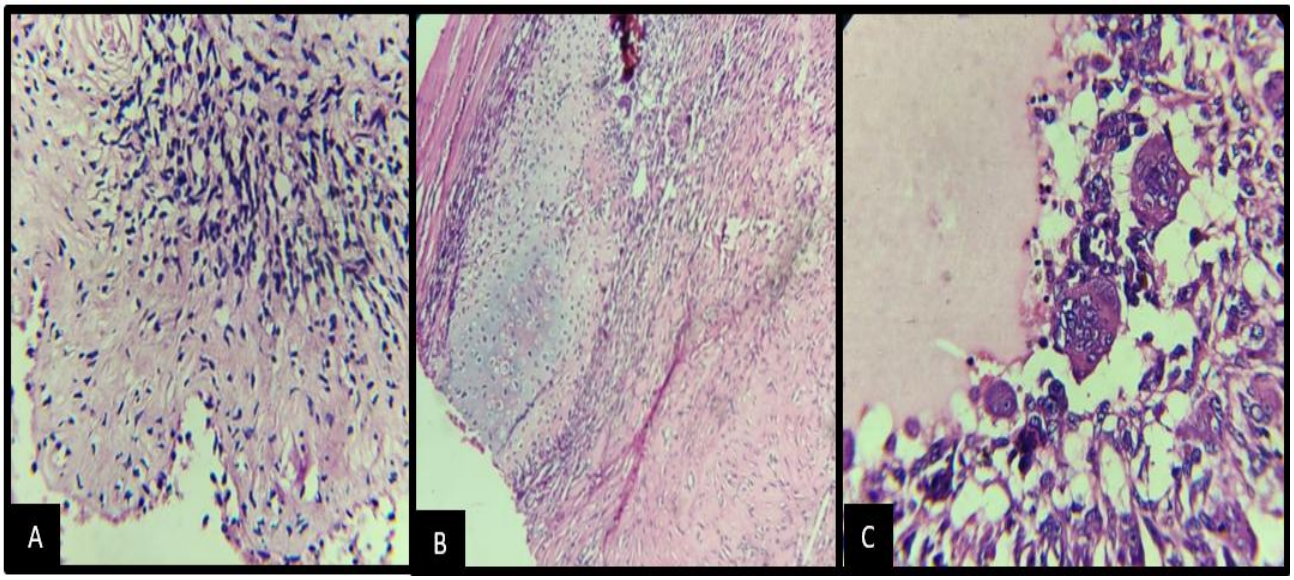

Figure 3: Microphotograph of a) phyllodes tumor b) Chondrosarcoma component c) Osteosarcoma component on histology (H & E, x400)

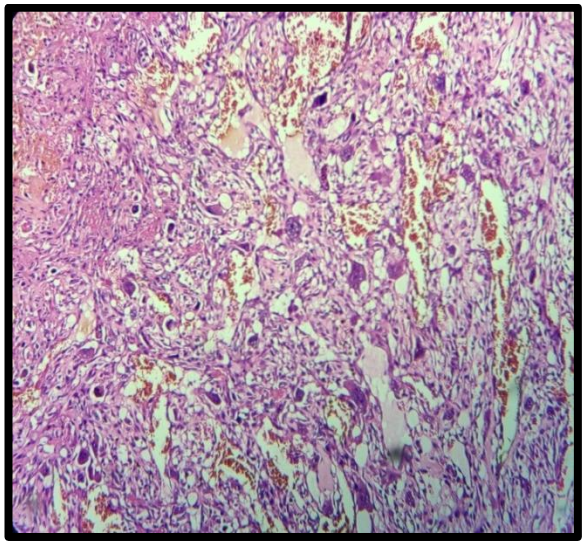

Figure 4: Microphotograph of malignant phyllodes tumor with angiosarcoma component on histology (H & E, x400)

Table 1: Summary of Malignant Phyllodes Tumor Cases with Heterologous Differentiation

Case	Age (years)	Presentation	Tumor Size (cm)	Quadrant	Heterologous Differentiation	Surgical Procedure	Margins	Follow-up Status
1	64	Gradually enlarging painless lump	5.2 × 3.5	Upper outer (Left)	Chondrosarcoma	Modified radical mastectomy + ALND	Negative	No recurrence at 18 months
2	59	Rapidly enlarging painless lump	6.4 × 4.3	Upper inner (Left)	Angiosarcoma	Modified radical mastectomy	Negative	No recurrence at 6 months
3	48	Progressive painless lump	4.8 × 4.1	Lower outer (Right)	Osteosarcoma + Chondrosarcoma	Modified radical mastectomy		Not documented (lost to follow-up)

Discussion

Malignant phyllodes tumors (MPTs) of the breast are rare fibroepithelial neoplasms, accounting for less than 1% of all breast tumors, with only a small subset demonstrating heterologous stromal differentiation. This variant is characterized by the presence of sarcomatous elements such as osteosarcoma, liposarcoma, chondrosarcoma, rhabdomyosarcoma, or angiosarcoma within the tumor stroma, which significantly alters the tumor's clinical behavior and prognosis [1, 2].

In our series, the patients presented in the fourth and fifth decades, consistent with the age distribution reported in the literature [3, 4]. All tumors were large (>8 cm), which is typical of malignant variants and often necessitates mastectomy rather than breast-conserving surgery [2]. The size of the tumor and stromal overgrowth are known predictors of malignancy and recurrence [5].

Histopathologically, the diagnosis of MPT with heterologous differentiation can be challenging, especially on core biopsies where the sampling may not capture the malignant or heterologous components. In our cases, osteosarcomatous, liposarcomatous, and angiosarcomatous differentiations were found. This aligns with reports by Punhani et al. [1] and Ahmed et al. [7], who emphasized the role heterologous elements from metaplastic carcinoma or primary breast sarcomas.

Management primarily involves wide surgical excision with negative margins, which remains the most important factor in reducing recurrence [6, 8]. However, despite surgical management, two patients experienced either local recurrence or distant metastasis within a year, highlighting the aggressive nature of heterologous variants has been observed in previous case series by Wang et al. [11] and Lim et al. [9], with recurrence rates as high as 40% in malignant cases with heterologous elements.

The role of adjuvant therapy in MPT remains controversial. While chemotherapy and radiotherapy have not consistently shown benefit, certain subtypes, may respond to sarcoma-based regimens [13, 15]. Nevertheless, evidence is limited and largely anecdotal.

Given the rarity of this variant, large prospective studies are not feasible, making case reports and series essential for expanding our understanding. Our experience underlines the importance of complete histopathological evaluation, appropriate immunohistochemical profiling, and individualized patient management, particularly in high-risk histological subtypes.

Future directions may include the exploration of molecular markers and genetic mutations that could serve as potential therapeutic targets or prognostic indicators, as suggested by Tang et al. [14]. Until then, meticulous pathological evaluation and multidisciplinary decision-making remains the cornerstone of management in this rare tumor subset.

Conclusion

This case series highlights the diverse histopathological presentations and clinical behavior of malignant phyllodes tumors with heterologous differentiation. Despite their rarity, these tumors pose significant diagnostic and therapeutic challenges due to their aggressive nature and potential for early recurrence and metastasis. The presence of heterologous elements such as osteosarcoma, liposarcoma, chondrosarcomatous or rhabdomyosarcoma within the stromal component is associated with a poorer prognosis and underscores the need for thorough histopathological evaluation. Surgical excision with wide, tumor-free margins remains the mainstay of treatment, while the role of adjuvant therapy requires further clarification. Early recognition, multidisciplinary management, and close follow-up are essential for improving outcomes. Continued reporting of such rare variants will aid in better understanding their biological behavior and may guide the development of more effective, individualized treatment strategies.

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