CASE REPORT

Malignant Phyllodes Tumors with Heterologous Differentiation - Two Interesting Cases

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ABSTRACT

Malignant phyllodes tumors represent rare but potentially aggressive form of breast neoplasm, comprising 0.3 to 0.9% of primary breast tumors. They infrequently exhibit heterologous mesenchymal differentiation. Here, we present two atypical cases of malignant phyllodes tumors- one displaying liposarcomatous differentiation and the other osteoclastic differentiation. These cases can be mistaken for metaplastic carcinoma of the breast. Distinguishing features are crucial, as it can be challenging to differentiate osteoclastic differentiation from fibrous histiocytoma and liposarcomatous differentiation from liposarcoma. However, careful histopathological examination and immunohistochemistry aid in reaching a definitive diagnosis. Accurate identification of these distinct rare entities is vital due to their prognostic significance.

KEY WORDS: Malignant phyllodes tumors, Liposarcomatous differentiation, Osteoclastic differentiation, Metaplastic carcinoma, Malignant Fibrous Histiocytoma, Liposarcoma.

Introduction

Phyllodes tumors (PTs) are rare fibroepithelial neoplasms of the breast, accounting for approximately 0.3 to 1.5% of all primary breast tumors.[1] They are classified as benign, borderline, or malignant based on histological features such as stromal cellularity, stromal atypia, stromal overgrowth, mitotic count, and tumor border.[2] This classification predicts clinical behaviour. Benign PTs are the most common (75.6-100%) and do not metastasize but may recur locally if incompletely excised. Borderline PTs account for 2.3-17.8%; and malignant PTs, representing 6.6-20%, have a higher potential for recurrence and metastasis and behave like sarcomas.[3]

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Malignant PTs are characterized by high stromal cellularity and nuclear pleomorphism, stromal overgrowth, and more than 10 mitoses per 10 high power field (HPF). Rarely, malignant PTs may show heterologous differentiation, such as liposarcoma, osteosarcoma, angiosarcoma, rhabdomyosarcoma, leiomyosarcoma, osteoclastoma, etc.[4,5]

In this report, the authors delineate two exceptionally uncommon and interesting cases of malignant phyllodes tumors, one exhibiting liposarcomatous differentiation and the other showcasing osteoclastic differentiation.

Case Report

Case 1

A 45-year-old female presented with a huge lump in left breast persisting for 6 months. Clinical examination revealed a left breast lump measuring 24×25cm involving the upper and lower inner quadrants. Based on clinical and radiological assessments, the diagnosis of phyllodes tumor was established, leading to subsequent simple mastectomy procedure. The excised mastectomy specimen measured 24×21×14cm, covered by intact skin,

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with two ulceroproliferative nodules measuring 9×9×4cm and 8×5×4cm respectively present on the skin surface (Figure 1**A**). The cut surface of the tumor exhibited solid to cystic consistency, displaying a variegated yellowish to grey appearance with variable sized cysts containing mucoid material (Figure 1 **B**).

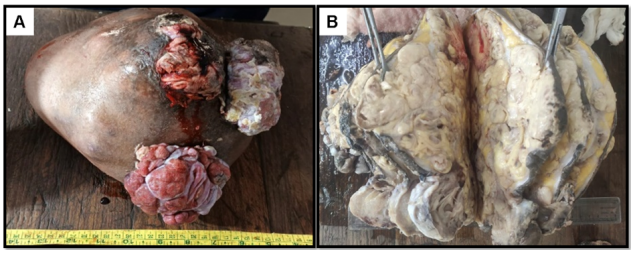

Figure 1: Gross specimen of malignant phyllodes tumor with liposarcomatous differentiation: (A) Large tumor mass involving whole left breast with two ulceroproliferative nodules over skin. (B) Cut surface shows solid to cystic, yellowish to grey variegated appearance

Microscopic findings revealed tumor with biphasic pattern with compressed glandular spaces, leaf like epithelial pattern, increased stromal cellularity with marked stromal atypia and mitotic count of 12-15/10HPF. Transition into adipocytes and multivacuolated lipoblasts were also present (Figure 2). Histopathological diagnosis of malignant phyllodes tumor with liposarcomatous differentiation was made.

On immunohistochemistry, tumor was diffusely immunoreactive for S100 protein and immunonegative for MDM2/CDK4 and Cytokeratin differentiating it from primary liposarcoma of breast (Figure 2).

Case 2

A 39 years old female, operated case of malignant phyllodes tumor of left breast 4 months back presented with recurrent tumor mass in same breast of size 10×10cm since 1 month. Subsequently, modified radical mastectomy (MRM) was performed. MRM specimen measured 13×12×7.5cm. External surface was covered with skin flap with presence of a horizontal scar 5 cm above nipple-areolar complex. On cut section, tumor was soft to firm, solid-cystic and grey to reddish brown in colour (Figure 3).

Microscopic findings revealed tumor mass showing slit like spaces lined by benign epithelium with malignant spindle cells arranged in fascicles with numerous uniformly distributed osteoclastic giant

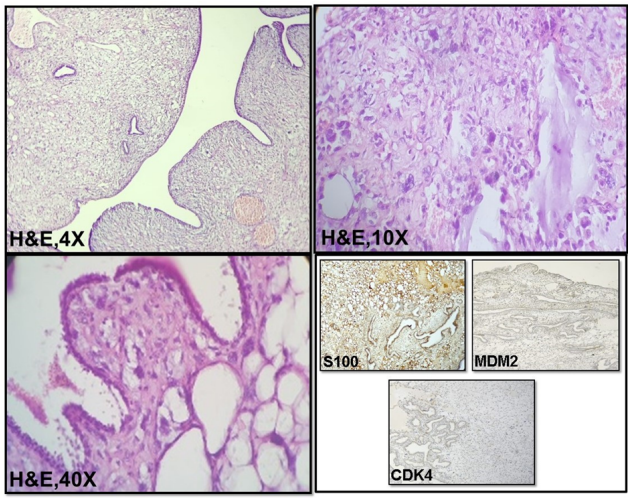

Figure 2: Microscopic picture of malignant phyllodes tumor with liposarcomatous differentiation: Tumor shows biphasic pattern with many leaf like intraglandular processes showing periductular condensation of spindle cell stroma. Transition into adipocytes and multivacuolated lipoblast present. Tumor is diffusly immunoreactive for S100 and immunonegative for MDM2/CDK4

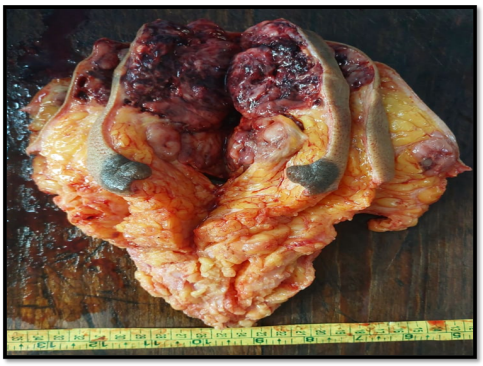

Figure 3: Gross specimen of malignant phyllodes tumor with osteoclastic differentiation: Modified radical mastectomy specimen showing large, grey to reddish-brown, soft to firm tumor mass. Cut surface is solid to cystic with areas of haemorrhage and necrosis

cells in the tumor. Stromal cells show moderate pleomorphism, hyperchromasia and mitotic count of 15-17/10HPF. Areas of haemorrhage and necrosis also seen (Figure 4). On immunohistochemistry, tumor was negative for ER, PR and Cytokeratin. Histopathological diagnosis of malignant phyllodes tumor with osteoclastic differentiation was made.

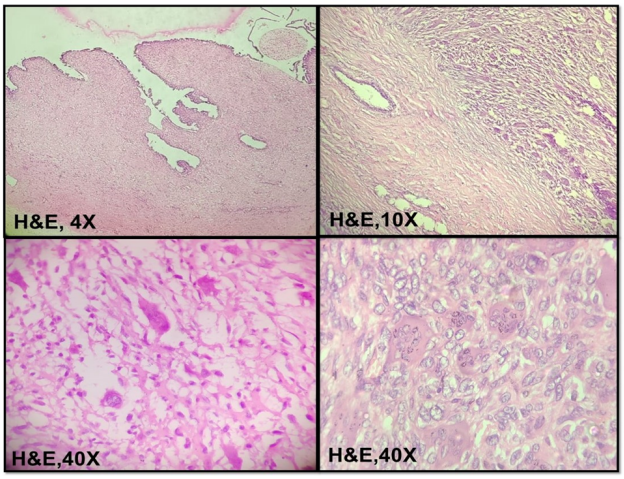

Figure 4: Microscopic picture of malignant phyllodes tumor with osteoclastic differentiation: Tumor mass shows malignant spindle cells arranged in fascicles with numerous uniformly distributed osteoclastic giant cells in the tumor. Stromal cells show pleomorphism, hyperchromasia, mitoses >10/10 HPF

Discussion

Phyllodes tumors commonly manifest as a firm, palpable, and mobile mass, characterized by rapid growth. Imaging studies typically reveal a well-defined, high-density mass exhibiting an oval, round, or lobulated morphology. On average, these tumors measure 4-5 cm in diameter, although their size can vary widely, ranging from 1 to 20 cm.[6]

The WHO classification of breast tumors is the standard for grading phyllodes tumors (PTs). Malignant PTs are characterized by: (I) Significant nuclear pleomorphism and stromal cell proliferation causing stromal overgrowth; (II) ≥10 mitoses per 10 high-power fields (0.5 mm diameter, 0.2 mm^2 area); (III) Increased stromal cellularity and invasive tumor margins; (IV) Presence of malignant heterologous elements, except well-differentiated liposarcoma, as a diagnostic marker even without presence of other features.[7]

Malignant PTs are often misdiagnosed as sarcomas or metaplastic carcinoma.[4] Differentiating these is crucial, as the 5-year survival rate for malignant PTs exceeds 91%, compared to less than 60% for metaplastic carcinoma.[3] Morphologically, metaplastic carcinoma exhibits spindle cells with nuclear pleomorphism, abundant mitotic figures and heterologous components, whereas phyllodes tumors show leaf-like architecture and a benign epithelial cell lining.[8] In both cases, metaplastic carcinoma was excluded as cytokeratin tested negative on immunohistochemistry.

The diagnosis of malignant phyllodes tumor with liposarcomatous differentiation in the first case, as opposed to primary liposarcoma of the breast, was based on gross observations of a solid tumor with cleft-like spaces and microscopic features such as myxoid stroma and slit-like compressed ducts displaying a leaf-like pattern, consistent with phyllodes tumors. This aligns with findings reported by Yusuf et al. Additionally, negativity for MDM2/CDK4 on immunohistochemistry aided in differentiating it from primary liposarcoma, which typically has a poorer clinical outcome and requires more aggressive treatment.[4]

Adipocytic differentiation in phyllodes tumors resembles well-differentiated liposarcoma but lacks typical MDM2 and CDK4 amplifications. Recent evidence suggests that relying solely on well-differentiated liposarcomatous differentiation is not advisable for diagnosing malignant phyllodes tumors due to low metastatic risk.[9] In our case, the diagnosis of malignant phyllodes is based on features like moderate stromal cellularity, high mitotic count, and absence of MDM2/CDK2 expression.

In the second case, the diagnosis of malignant PT with osteoclastic differentiation resembled malignant fibrous histiocytoma (MFH). However, MFH was ruled out due to absent storiform pattern and adjacent benign leaf-like foci characteristic of PTs, consistent with findings by Vani et al. Multinucleate osteoclastic giant cells observed are non-neoplastic, likely modified histiocytes responding to tumor's extracellular matrix.[3]

The recurrence and metastasis of phyllodes tumors correlate with their histological grade. Benign tumors rarely recur or metastasize, while malignant tumors are prone to both if not widely excised.[4] A 1 cm surgical margin is standard but often leads to poor cosmetic outcomes, making total mastectomy a viable option.[8] Sentinel node biopsy is unnecessary due to the rarity of lymph node metastasis, and adjuvant radiation and chemotherapy do not improve survival in malignant cases.[10]

Conclusion

Histopathological examination complemented by immunohistochemistry, facilitated the establishment

of a conclusive diagnosis of malignant phyllodes tumors with heterologous differentiation. The identification and distinction of these rare entities from their closely resembling counterparts hold significant importance due to their implications for prognosis.

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