

# Pleomorphic Sarcoma of Breast: A Report of Two Cases and Review of Literature

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**Abstract-** Sarcomas account for less than 1% of all primary breast malignancies, pleomorphic sarcoma of the breast being even rarer. We present two cases of pleomorphic sarcoma of the breast in a 35-year-old and a 43-year-old female. An extensive review of the available literature with evaluation of the etiology, changing terminologies and histopathologic features of pleomorphic sarcoma of the breast are discussed. The prognostic factors and treatment modalities have also been reviewed.

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**Keywords:** Pleomorphic; Sarcoma; Breast

## Introduction

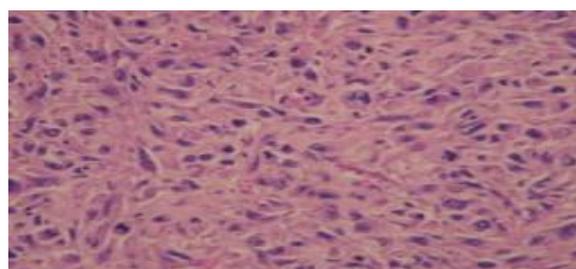
The concept of Malignant fibrous histiocytoma (MFH) was first introduced by O'Brien and Stout in 1964 (1). MFH is a common tumor in the deep soft tissues. It is a soft tissue sarcoma composed of fibroblast-like and histiocyte-like cells, mixed with pleomorphic giant and inflammatory cells. The most frequent primary sites include the lower (49%) and upper (19%) limbs, and the retroperitoneum and abdomen (16%). Localization in the breast is extremely rare, accounting for less than 1% of all breast primary malignancies (2). So far, only 65 cases of breast MFH have previously been reported (3). Knowledge of this entity is of utmost importance to distinguish it from undifferentiated carcinoma and other pleomorphic sarcomas. Establishment of correct diagnosis is quintessential for appropriate management as it is a very aggressive tumor with a high rate of recurrence and distant metastases. Herein, we present two cases of breast MFH and review the prior literature with an analysis of clinicopathological features, prognostic factors, and treatment strategies.

## Case Report

### Case 1

A 35-year-old female came with the complaint of a large lump in the right breast. There was no significant medical or family history. On physical examination, a

large 17x15 cm fungating and profusely bleeding growth was found in the upper outer quadrant of the right breast. Ultrasound examination revealed a large lobulated, highly vascular hypoechoic multicystic lesion in the upper outer quadrant. On FNAC, diagnosis of malignancy was given, and thus a modified radical mastectomy was performed. On gross examination, almost entire breast parenchyma was replaced by a gray, white tumor measuring 18x16x9 cm. Histological examination revealed a highly cellular tumor composed of oval to spindle-shaped cells, arranged in interlacing bundles, fascicles, and sheets (Figure 1). The focal whirling pattern was also seen.



**Figure 1.** Fascicles of oval to spindle-shaped cells showing brisk mitosis, no epithelial component seen (H and E x 200)

Tumor cells showed marked nuclear pleomorphism and moderated to the abundant eosinophilic cytoplasm (Figure 2). Large areas of necrosis and brisk mitosis were noted.

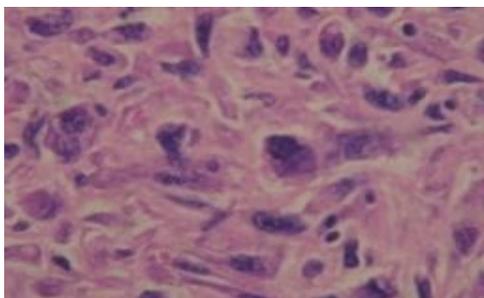
On extensive sampling, there was no epithelial component. On immunohistochemistry, the tumor cells

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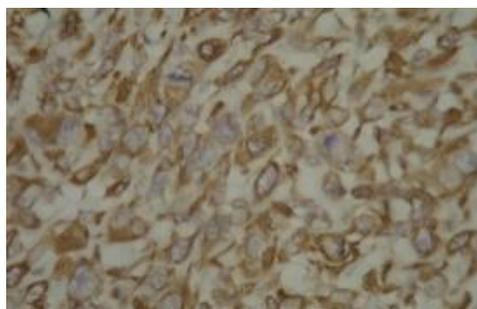
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were positive for vimentin (Figure 3) and CD68 (Figure 4), and negative for cytokeratin (Figure 5), SMA, S-100, and desmin.

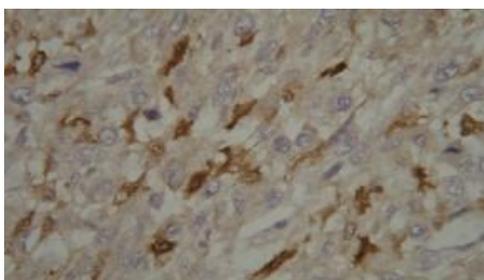
Lymph nodes isolated were free from tumor infiltration. A diagnosis of high-grade sarcoma, with features of pleomorphic sarcoma, was made.



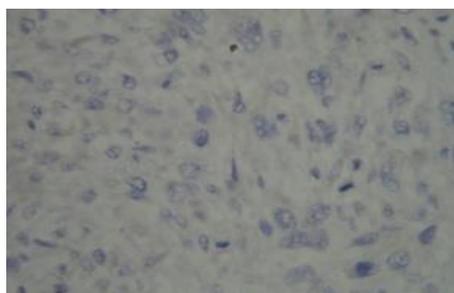
**Figure 2.** Tumor cells showing nuclear hyperchromasia and marked nuclear pleomorphism (H and E x 400)



**Figure 3.** Tumor cells showing vimentin positivity in cytoplasm (x 400)



**Figure 4.** Tumor cells showing CD 68 positivity in cytoplasm (x 400)



**Figure 5.** Tumor cells were negative for Cytokeratin

## Case 2

A 43-year-old female with no significant previous medical or family history, presented with a mass in her left breast, discovered by the patient 3 months ago. Upon physical examination, a 1-cm skin area of retraction was identified in the upper outer quadrant of her left breast corresponding to an ill-defined, solid mass, 3.5 cm in diameter, slightly painful on palpation.

Axillary lymph nodes and right breast were unremarkable. Mammographic studies showed a retro-areolar, dense mass, around 4 cm diameter with indistinct margins. No microcalcification was seen. On FNAC, a diagnosis of malignancy was given. Subsequently left modified radical mastectomy was performed. The histological sections showed a mesenchymal neoplasm composed primarily of interlacing bundles and fascicles of tumor cells. The tumor cells were large oval to spindle shaped cells with pleomorphic nuclei and abundant eosinophilic cytoplasm. Many tumor giant cells were seen interspersed within the tumor. Many atypical mitotic figures and extensive areas of necrosis were seen. Immunohistochemistry revealed vimentin and CD68 positivity in tumor cells, while the tumor cells were negative for CK, SMA, S-100 and desmin. All axillary lymph nodes removed were free from metastasis. Thus a diagnosis of breast sarcoma, pleomorphic sarcoma type was rendered.

## Discussion

Non-epithelial tumors of the breast account for less than 1% of all primary breast malignancies (2). These lesions can be generically defined as "sarcomas," comprising all malignancies arising from the connective tissue of the gland. However, according to Pollard, cases of the malignant phyllodes tumor should be excluded from soft tissue sarcomas of the breast because it is a distinct clinicopathological entity (4).

Although the precise histogenesis of the tumor remains unclear, the probable origin is from the tissue histiocyte which is capable of acting as a facultative fibroblast. It has also been suggested that it is a primitive mesenchymal tumor showing a capability of dual differentiation towards fibroblast or histiocyte. MFH of the breast may either arise "*de novo*" from the connective tissue of the gland or develop in a breast after irradiation for carcinoma, for which the term "post-radiation sarcoma" of extraglandular origin is used. Post radiation sarcomas of the breast that have been reported

## Pleomorphic sarcoma of breast

in the literature include angiosarcoma, osteosarcoma, fibrosarcoma, and MFH (5). Very few cases of breast MFH have been reported in the English literature.

There has been an increase in the development of these sarcomas in the last decade. According to Sheppard, this may be explained by the increasing popularity of breast-sparing surgery followed by irradiation in the treatment of breast carcinoma (6). The criteria for radiation-induced sarcoma includes a prior history of radiation, the latency of 3-4 years or more, development of the sarcoma near to or within a previously irradiated field, and a histological diagnosis of sarcoma (7). Data from various studies has suggested a relative risk of about 2.1 to 2.3 for second malignant sarcoma in all breast cancer survivors (8,9). For patients receiving radiotherapy, the cumulative incidence of second malignant sarcoma was 3.2 per 1,000 at 15 years compared to 2.3 per 1,000 in patients not receiving radiotherapy (7). Both of our cases were *de novo* without any prior history of radiation therapy.

According to Smith *et al.*, primary breast sarcoma has imaging features that are not typically seen in infiltrating ductal carcinoma (10). Mammographic features are of a large non-calcified, oval mass with indistinct margins. At sonography, most primary breast sarcomas are oval solid hypervascular, hypoechoic masses with posterior acoustic enhancement.

As the histogenesis of MFH still remains controversial, tumor morphology becomes more important than histogenesis for diagnosis of MFH. These tumors usually consist of fibroblast-like and histiocytic-like cells, mixed with pleomorphic giant and inflammatory cells. MFH shows features spanning a wide spectrum of histological patterns, falling essentially into 4 principal variants on the basis of the criteria assessed by Weiss- Enzinger and Kearney (11). These are the storiform-pleomorphic MFH (the most frequent), the giant-cell type (pleomorphic), the myxoid type and the inflammatory type. According to the most recent 2013 WHO classification of soft tissue tumors, a major change has been the final removal of the term 'malignant fibrous histiocytoma' which, in 2002 edition, was admitted to be a diagnosis of exclusion, synonymous with undifferentiated pleomorphic sarcoma. These are now included in a separate and new category of undifferentiated/unclassified sarcomas (12).

MFH needs to be distinguished from undifferentiated carcinomas and other sarcomas which show a similar

degree of cellular pleomorphism. The differential diagnoses include malignant phyllodes tumor, carcinosarcoma, pleomorphic leiomyosarcoma, pleomorphic liposarcoma, malignant peripheral nerve sheath tumor, osteosarcoma and pleomorphic rhabdomyosarcoma (11,13). A definitive diagnosis is based on careful histopathological and immunohistochemical examination. Extensive sampling should be done to rule out invasive ductal carcinoma and normal ductal components, the presence of which is suggestive of carcinosarcoma and malignant phyllodes tumor respectively. Lipoblasts, whose presence is necessary for the diagnosis of liposarcoma, should be looked for to exclude liposarcoma. Leiomyosarcoma usually has small areas with conventional smooth muscle cytomorphology and a fascicular growth pattern. Additionally, leiomyosarcoma usually shows positive cytoplasmic expression of SMA in the tumor cells. The alveolar pattern of tumor growth and presence of rhabdomyoblasts showing striations is suggestive of a diagnosis of rhabdomyosarcoma. Immunohistochemical staining with desmin is used as a specific marker for rhabdomyosarcoma. Pure osteosarcoma of the breast is extremely rare, and many cases of this disease show osteosarcomatous elements within metaplastic carcinomas. Table 1 elaborates the various differential diagnoses with their histopathologic and immunohistochemical features.

The treatment of choice for MFH of the breast is surgery. The standard therapy is mastectomy which should include the excision of both underlying pectoral muscles, in order to reduce the rate of local recurrence (3,4). Other approaches include a breast-preserving wide local excision (WLE) with adequate negative margins, particularly for smaller tumors less than 5 cm (14).

MFH cells rarely spread via lymphatic vessels, regional lymph node involvement being low (12-29%). Therefore, axillary lymph node dissection in breast MFH seems unjustifiable (15). The role of chemotherapy and radiation therapy has not been clearly defined in its management (16). Although some authors believe that preoperative radiotherapy could achieve slight regression of both the primary tumor and metastasis to the axillary lymph node, Blanchard *et al.*, do not recommend radiotherapy after clear cancer-free surgical margin operation (17).

**Table 1. Differential diagnosis of malignant mesenchymal tumors of breast**

Differential diagnosis	Histopathologic features	Immunohistochemical features
<b>Malignant phyllodes tumor</b>	Stromal hypercellularity, cellular atypia, and high mitotic rate along with presence of normal ductal elements	Vimentin positive CD34 +/- , SMA +/-
<b>Metaplastic carcinoma</b>	High grade poorly differentiated ductal carcinoma with high-grade sarcomatous component	Epithelial component: CK positive; Mesenchymal component: vimentin positive
<b>Pleomorphic leiomyosarcoma</b>	Fascicles of atypical spindle cells with cigar-shaped hyperchromatic nuclei and eosinophilic cytoplasm	SMA and desmin positive
<b>Pleomorphic rhabdomyosarcoma</b>	Large, pleomorphic rhabdomyoblasts with cytoplasmic cross-striations	Desmin, myogenin, and MyoD1 positive
<b>Osteosarcoma</b>	Predominance of malignant osteoid, which is irregular with a lacelike filigree pattern	--
<b>Pleomorphic liposarcoma</b>	Characterized by bizarre giant lipoblasts	Maybe immunoreactive for S-100 protein
<b>Malignant peripheral nerve sheath tumor</b>	Cellular tumor characterized by pleomorphic cells with wavy nuclei, prominent mitotic activity and areas of tumor necrosis	Less strongly positive for S-100 protein
<b>Malignant fibrous histiocytoma/ undifferentiated pleomorphic sarcoma</b>	Malignant proliferation of giant cells, histiocytes, fibroblasts, and myofibroblasts arranged in a storiform pattern	Vimentin positive, CD68 typically positive

MFH of the breast is a very aggressive tumor, fast growing with a high rate of local recurrence (44%) and distant metastases (42%), particularly in the lungs (82%), bony skeleton, pleura, and liver; regional lymph nodes involvement ranges from 12% to 32%. Blanchard *et al.*, report that the median survival of patients with breast MFH is 58 months, but there is no correlation between the size of the primary tumor and the risk of recurrence or death from disease (2). Due to the low incidence of the disease, the prognostic factors for breast MFH remain unclear (3,14). However, deep and large tumors have been found to be associated with poor prognosis, while tumors with a prominent acute or chronic inflammatory component or those displaying highly myxoid forms of MFH have a better prognosis. The percentages of survival reported in the literature range from 40 to 60% after 2 years, and from 20 to 35% after 5 years (14). Biological markers, especially Ki-67, are widely used as prognostic markers in breast cancers (3). Patients with high Ki-67 expression have been shown to have a dramatically shorter life span than those with low Ki-67 expression, higher risk of local recurrence, distant metastasis, and poor prognosis in MFH of the breast (3).

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