

CASE REPORT

Undifferentiated Pleomorphic Sarcoma of the Male Breast Causing Diagnostic Challenges

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Undifferentiated pleomorphic sarcoma of the breast are uncommon and often present diagnostic challenges. Herein, we report a case of the undifferentiated pleomorphic sarcoma occurring in the male breast. A 76-year-old man presented with a palpable bean-sized mass in his left breast for two months. Core needle biopsy revealed the presence of atypical cells in a fibrous proliferative lesion, which was removed by wide excision. Based on examination of the excised tumor, the initial pathologic diagnosis was atypical spindle cell lesion with uncertain malignant poten-

tial. One year later, the patient returned with a recurrent mass at the previous surgical site. The mass was again surgically removed using wide excision. Based on histological findings with immunomarkers, the final diagnosis was undifferentiated pleomorphic sarcoma. Undifferentiated pleomorphic sarcoma of the breast can cause genuine diagnostic difficulty and appropriate immunohistochemistry is mandatory for differential diagnosis.

Key Words: Breast neoplasms, Male, Malignant fibrous histiocytoma, Sarcoma

INTRODUCTION

Primary breast sarcomas are rare, histologically heterogeneous nonepithelial malignancies that arise from the connective tissue within the breast [1]. Like soft tissue sarcomas originating in other parts of the body, breast sarcomas consist of a heterogeneous group of several subtypes: liposarcoma, fibrosarcoma, pleomorphic sarcoma, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma, and osteosarcoma, sarcomas of uncertain differentiation [2].

Undifferentiated pleomorphic sarcoma has been defined as a group of pleomorphic, high-grade sarcomas in which any attempt to disclose their line of differentiation has failed. It constitutes less than 5% of all sarcomas in adults [3] and has been rarely seen in breast [4]. The clinical features of this rare tumor mimic those of breast carcinoma and often presents diagnostic challenges [5].

Herein, we report a case of primary undifferentiated pleo-

morphic sarcoma in a 76-year-old man; this case highlights a rare and interesting variant of primary breast sarcoma and the diagnostic difficulty that physician and pathologist may encounter with it.

CASE REPORT

We report a case of spindle cell sarcoma of the breast in a 76-year-old man. He presented to the Daegu Catholic University Hospital with a lump in his left breast that had been present for the previous two months. He had been taking medication for hypertension and benign prostate hypertrophy and had not suffered trauma to his chest wall. Further, he had no family history of malignancy, including breast cancer.

On physical examination, the patient had a poorly demarcated, mobile, firm mass in his left breast. The mass was nontender, approximately 1 cm in diameter, and was detected in the subareolar area of the left breast. There was no clinical evidence of regional lymphadenopathy, and there were no abnormal findings in the right breast. Mammography revealed a dense lesion occupying the subareolar region; this lesion was consistent with prominent fibroglandular tissue and suggested asymmetric left gynecomastia (Figure 1A). Ultrasonography revealed a poorly demarcated and highly suspicious malignant lesion in the periareolar area of his left breast, and the lesion was categorized according to Breast Imaging Report and Data System

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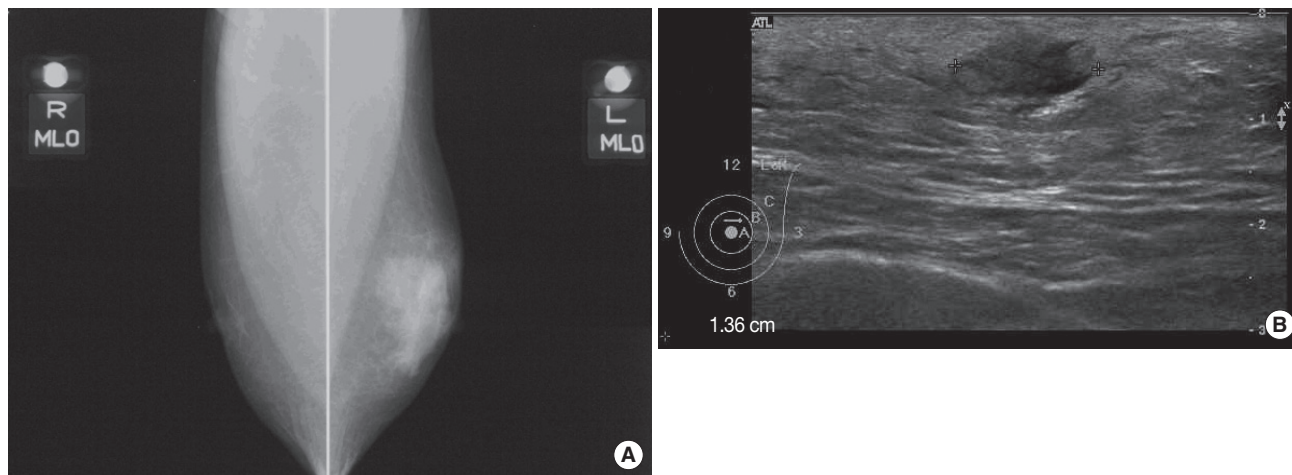


Figure 1. Initial radiologic findings. (A) Mammography showing prominent fibroglandular tissue in the subareolar area of left breast. (B) Ultrasonographic scan showing heterogeneous hypoechoic lesion with diffuse skin thickening and fatty infiltration.

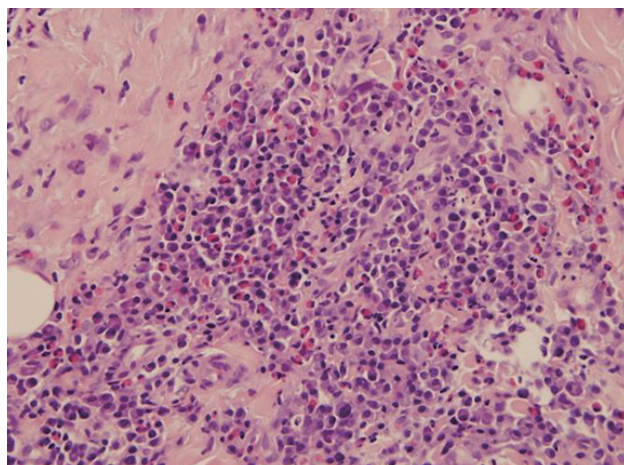


Figure 2. Histological findings of the left breast mass by core needle biopsy. Marked infiltration of plasma cells and eosinophils have been shown. Many atypical cells with large nuclei in the abundant collagenous stroma can be seen (H&E stain, $\times 400$).

(BIRADS) as BIRADS 4C (Figure 1B). He underwent ultrasound-guided core needle biopsy, which indicated the presence of atypical cells in the fibrous, proliferative lesion (Figure 2). Preoperative examination consisted of a complete blood count, serum kidney and liver function test, thyroid function test, and tests for the levels of several hormones related to the development of gynecomastia, including estrogen, testosterone, prolactin, and gonadotrophic hormones. All results were within the normal limits.

The patient underwent wide excision of the lesion, including removal of normal breast tissue to provide a safety margin and he did not require subsequent axillary lymph node dissection. Gross examination of the specimen revealed a whitish, fibrotic nodular lesion, measuring 1.5×1 cm in size including surround-

ing adipose tissue. The specimen was fixed in 10% formalin. Paraffin sections were prepared and stained with haematoxylin and eosin (H&E). Microscopic examination of the sections from the specimen showed nodular proliferation of fibrous tissue with focal infiltrating margins (Figure 3A). There were no ductal components and epithelial tissues. The nodules were composed of plump to spindle-shaped fibroblasts, many lymphoplasmic cells, eosinophilic infiltrate, and many keloid-like collagen bundles (Figure 3B). A few atypical multinuclear giant cells and pleomorphic cells were noted; however, abnormal mitosis was not identified. Immunohistochemical staining for desmin, smooth muscle actin (SMA), and S-100 protein was negative (Figure 3C). These diverse histological and immunohistochemical findings established the diagnosis of atypical spindle cell lesion with uncertain malignant potential, exhibiting features of a reactive fibroblastic lesion.

The patient's progress was monitored after the operation, and no specific adjuvant treatment was administered. One year later, he returned with a recurrent mass at the previous surgical site. On physical examination, a firm mass of about 2 cm in diameter was palpated in the wound from the previous surgery. Radiological studies, including computed tomography (CT) and positron emission tomography-CT (PET-CT), were conducted, and PET-CT showed faint fluorodeoxyglucose uptake in the area of the left breast that corresponded to the lesion seen on the CT scan (Figure 4). There was no evidence of either regional lymphadenopathy or distant metastasis. The lesion was surgically removed using wide excision.

A histological assay showed that the recurrent tumor was 3.8 cm sized in diameter and had an irregular margin. On sectioning, the cut surface showed fibrous bands and lobular adipose tissue with focal congestion without necrosis. The nodules

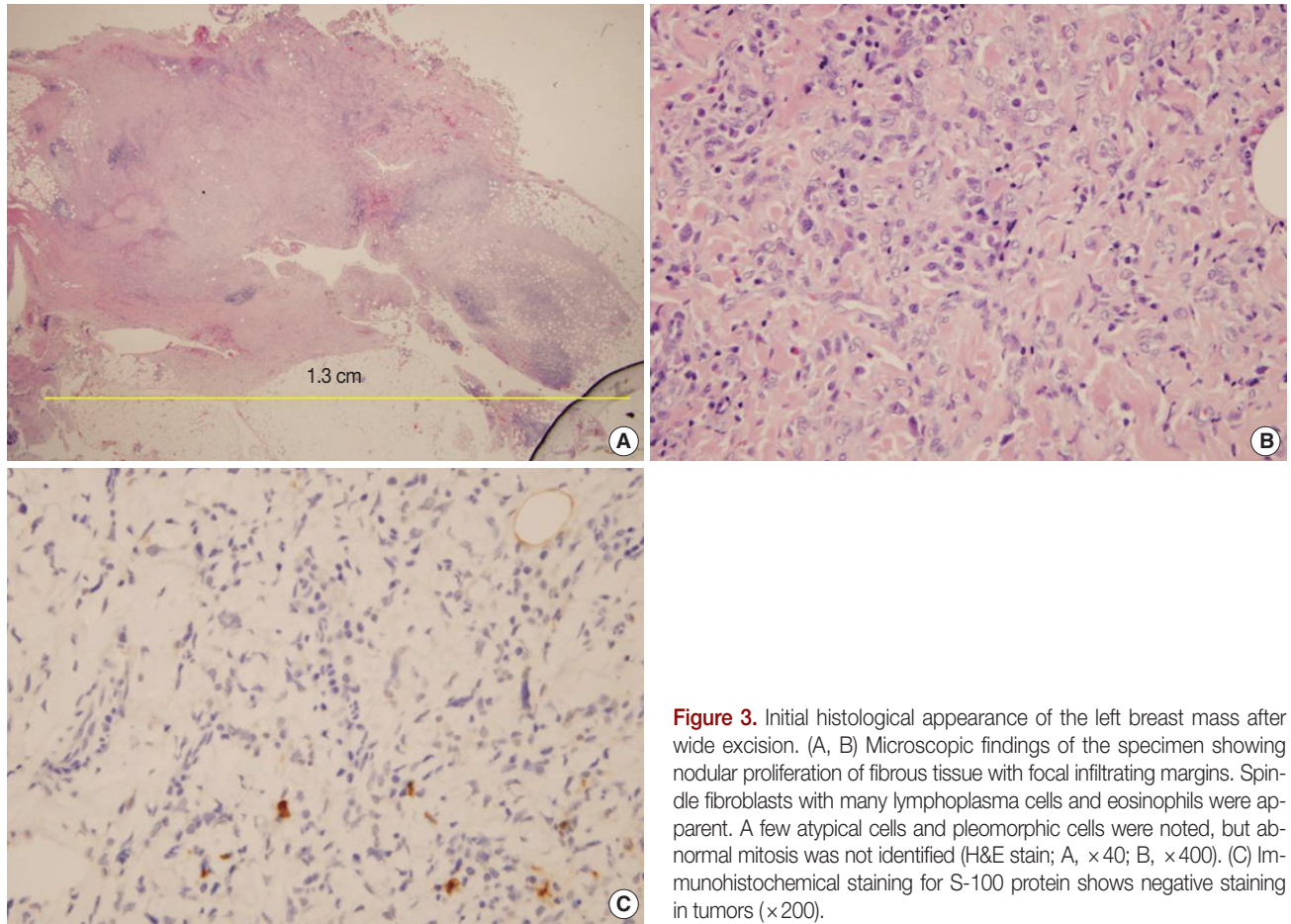


Figure 3. Initial histological appearance of the left breast mass after wide excision. (A, B) Microscopic findings of the specimen showing nodular proliferation of fibrous tissue with focal infiltrating margins. Spindle fibroblasts with many lymphoplasmic cells and eosinophils were apparent. A few atypical cells and pleomorphic cells were noted, but abnormal mitosis was not identified (H&E stain; A, $\times 40$; B, $\times 400$). (C) Immunohistochemical staining for S-100 protein shows negative staining in tumors ($\times 200$).

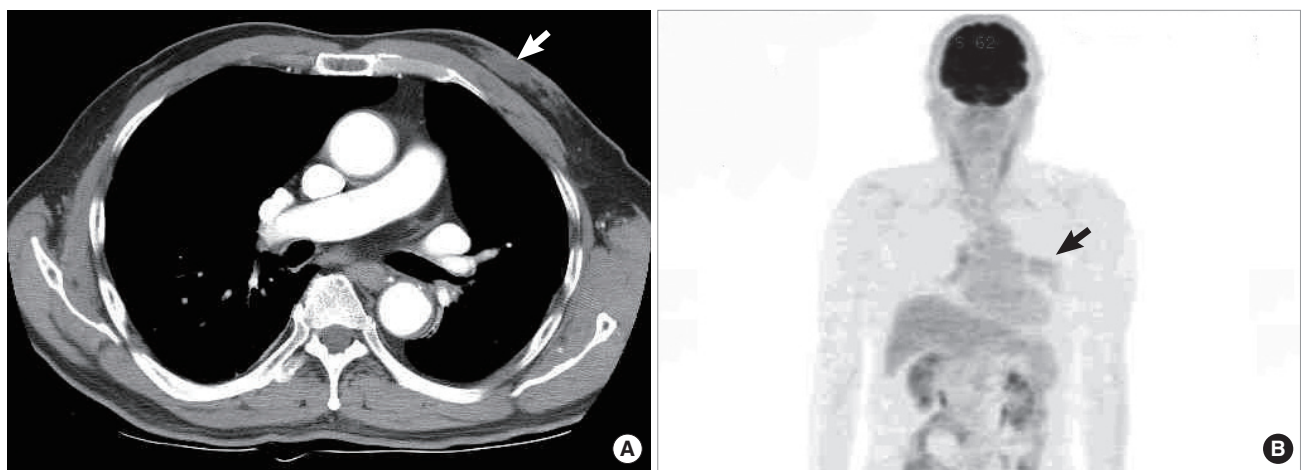


Figure 4. Radiologic findings of a recurrent mass in left breast. (A) Computed tomography (CT) image showing a low attenuating mass in the subareolar area of the left breast (arrow) without significant lymph node enlargement. (B) Positron emission tomography-CT image showing faint FDG uptake area in the left breast (arrow) without other metabolically significant FDG uptake lesions that would suggest axillary nodal or distant organ metastasis.

were composed of plump to spindle-shaped fibroblasts, many lymphoplasmic cells, eosinophilic infiltrate, and many keloid-like collagen bundles. Microscopic findings were similar to the

previous histological findings (Figure 5A), but many atypical cells and abnormal mitotic activity ranging from 6 to 10 mitotic figures per 10 high power fields (hpf) were noted and the re-

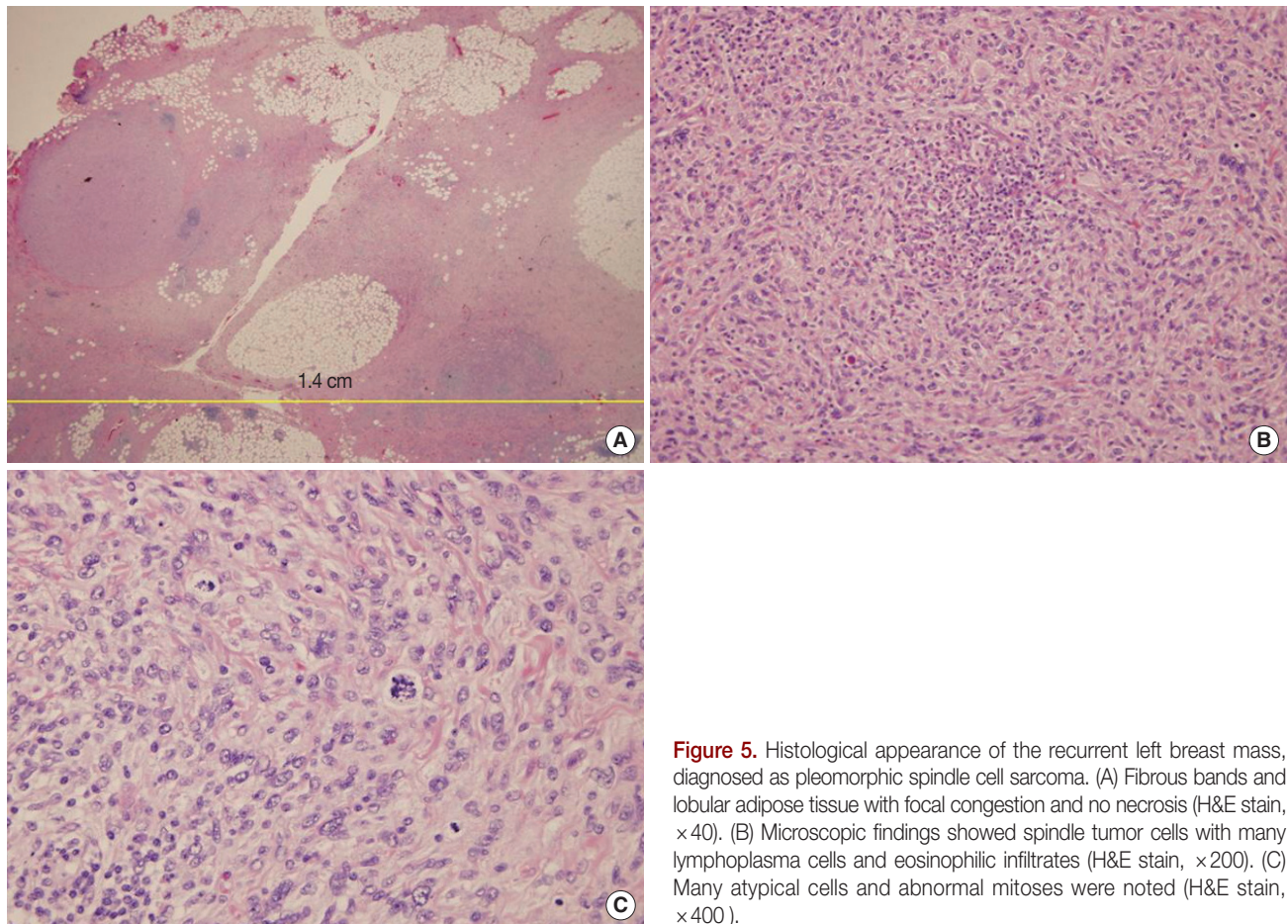


Figure 5. Histological appearance of the recurrent left breast mass, diagnosed as pleomorphic spindle cell sarcoma. (A) Fibrous bands and lobular adipose tissue with focal congestion and no necrosis (H&E stain, $\times 40$). (B) Microscopic findings showed spindle tumor cells with many lymphoplasmic cells and eosinophilic infiltrates (H&E stain, $\times 200$). (C) Many atypical cells and abnormal mitoses were noted (H&E stain, $\times 400$).

sected margins were involved with the tumor (Figure 5B, C). Based on the rapid recurrence of the mass, increase in tumor size, high degree of cellularity, presence of atypical cells, many abnormal mitotic figures, and infiltrating growth pattern, malignancy was indicated. The immunohistochemical staining for CD34 showed focal positivity; however, the cells were not reactive for other immunomarkers including cytokeratin (CK), epithelial membrane antigen (EMA), SMA, murine double-minute protein 2 (MDM2), desmin, S-100 protein, CD68 and anaplastic lymphoma kinase (ALK). These established histological features of malignant pleomorphic spindle cell tumor in addition to the immunohistochemical results demonstrated no line of differentiation and led to the diagnosis of undifferentiated pleomorphic sarcoma of the breast. Due to the involvement of the resected margin, the patient underwent simple mastectomy.

DISCUSSION

Primary breast sarcoma is a rare type of cancer arising from the mesenchymal tissue of the breast and represents less than

1% of all breast malignancies. It includes a heterogeneous group of disease entities. According to the World Health Organization (WHO) classification, malignant fibrous histiocytoma (MFH) is a morphological pattern rather than a distinct clinicopathological entity. Many neoplasms diagnosed as MFH previously are actually classified as pleomorphic subtypes of other sarcomas [2]. Pleomorphic MFH/undifferentiated pleomorphic sarcoma is defined as a group of pleomorphic, high-grade sarcomas showing no line of differentiation.

Undifferentiated pleomorphic sarcoma has been a diagnosis of exclusion following thorough sampling and critical use of ancillary diagnostic techniques. In the previous reports, it consisted of 10.5-24% of all primary breast sarcomas [4,6]. Most undifferentiated pleomorphic sarcomas have appeared in patients who are in their sixth and seventh decade of life [2]. Neither the symptoms nor the physical findings of undifferentiated pleomorphic sarcoma of the breast present any characteristic pattern that would easily suggest the diagnosis. Immunohistochemistry may be useful to distinguish primary breast sarcomas from non-mesenchymal malignant tumors and to delineate the level of differentiation of primary breast sarco-

mas [5]. Desmin, vimentin, smooth muscle antigen, CK, leukocyte common antigen, CD34, HMB-45, SMA, EMA, and S-100 protein should all be analyzed in sarcoma patients.

Undifferentiated pleomorphic sarcomas often grow rapidly and then may be painful. Imaging methods and macroscopy have revealed well-circumscribed masses with heterogeneous composition. Further, they have been identified as pale fibrous and fleshy areas admixed with zones of (cystic) necrosis, hemorrhage, or myxoid features [7]. Microscopically, lesions exhibit cells showing marked pleomorphism admixed with bizarre giant cells, spindle cells, and variable foamy cells [8]. A storiform growth pattern and variable chronic inflammatory cells are also common [7].

Limited data on undifferentiated pleomorphic sarcoma have indicated that this neoplasm has an aggressive clinical course and high incidence of recurrence and metastasis. Overall 5-year survival of patients with undifferentiated pleomorphic sarcoma has been roughly 50% [7]. Local surgical resection is the choice of treatment and negative margins are particularly important, although the extent of the surgery has been controversial. Axillary dissection has been generally thought to be unnecessary for undifferentiated pleomorphic sarcoma of the breast, since these tumors rarely metastasize via the lymphatics [9,10]. The role of adjuvant chemotherapy and radiation also has been unclear [9,10]. In our case, the patient was subjected to wide local excision for recurrent mass without axillary dissection and will undergo simple mastectomy due to involvement of the resected margin.

Differential diagnosis should include metaplastic (sarcomatoid) carcinoma, malignant phyllodes tumor, inflammatory myofibroblastic tumor (IMT), and myofibrosarcoma.

Metaplastic (sarcomatoid) carcinoma, also called spindle cell carcinoma, is a rare heterogeneous neoplasm generally characterized by a mixture of adenocarcinoma with dominant areas of spindle cells, squamous and other mesenchymal differentiation [11]. CK positivity of the spindle cells confirms the epithelial origin of this tumor.

Malignant phyllodes tumor consists of malignant mesenchymal cells and a benign epithelial component [5]. The tumor shows overgrowth of the stroma in relation to the epithelial component, cellular pleomorphism with sarcomatous elements and frequent mitoses, and invasion of the surrounding tissues. The tumor can be differentiated from undifferentiated pleomorphic sarcoma by more extensive sampling for identifying epithelial component.

IMT is a neoplasm of myofibroblastic origin, often admixed with prominent inflammatory infiltrate consisting of lymphocytes, plasma cells, macrophages, eosinophils and histiocytes. An IMT is a low-grade neoplastic lesion showing lack of atyp-

ia, hyperchromasia, and abnormal mitotic figures [12]. Immunohistochemistry of IMT shows strong SMA reactivity within the spindle cells frequently and occasional immunoreactivity for ALK, and negative or focal positivity for pankeratin.

Myofibrosarcomas are malignant tumors of myofibroblasts. Electron microscopy examination has been considered a gold standard for diagnosis of myofibrosarcoma, and ultrastructurally, the neoplastic cells have variable rough endoplasmic reticulum (RER) as well as peripheral filament bundles resembling stress fibers, collagen secretion granules and, rarely fibronectin fibrils and a fibronexus junction [13]. Most myofibrosarcomas are immunoreactive for SMA and expression of CK, EMA, CD34, desmin or S100 protein is seen sporadically.

Although rare, benign spindle cell lesions of the breast may show malignant progression as in our case; however, breast sarcoma may be misdiagnosed as benign spindle cell lesions such as myofibroblastoma, nodular fasciitis and fibromatosis. The histological criteria for the diagnosis of benign spindle cell neoplasms includes well-circumscribed cells, monomorphic, bland-looking spindle to oval-shaped cells, minimal to moderate cytological atypia, fascicular and/or haphazard growth pattern; absence of epithelial and myoepithelial components; mitotic activity of 2 or less per 10 hpf, and the absence of both atypical mitosis and necrosis [14].

Myofibroblastoma is a benign prototypic tumor of mammary stroma [13]. Currently, it is believed that myofibroblastoma occurs mainly in older men and postmenopausal women. Morphologic features of classic-type myofibroblastoma are purely mesenchymal tumor with no epimyoepithelial components, interspersed thick hyalinized collagen bundles, low mitotic count, lack of marked cytologic atypia, no atypical mitoses, and the absence of necrosis. Most myofibroblastomas are typically positive to vimentin, desmin, and CD34 and immunoreactivity for SMA, bcl-2, and CD99 is frequently obtained [13].

Nodular fasciitis is a rapidly growing lesion, which is usually subcutaneous and does not reach a large size. Microscopically, the lesion is fairly well circumscribed. It consists of plump active fibroblasts and myofibroblasts arranged in short, loose and irregular bundles. Nodular fasciitis is less cellular and uniform than undifferentiated pleomorphic sarcoma and does not infiltrate into surrounding tissue. Unlike in undifferentiated pleomorphic sarcoma, nuclear atypia and necrosis are not seen [5,14].

Fibromatosis is non-encapsulated well-differentiated fibroblastic lesion composed of relatively uniform fibroblasts and collagen forming a firm, solitary, or multinodular mass with an infiltrative growth pattern. Immunohistochemically, fibromatosis exhibits positivity for SMA and vimentin and negativity

for CK, estrogen, progesterone and androgen receptors [15].

In our case, the histological sections of the initially excised tumor showed nodular proliferation of fibrous tissue with focal infiltrating margins; and it was composed of plump to spindle-shaped fibroblasts, eosinophilic infiltrates, many lymphoplasmic cells, many keloid-like collagen bundles, a few atypical cells, including multinuclear giant cells and pleomorphic cells. The lack of abnormal mitosis was pointed towards a benign spindle cell lesion, and negative immunoreactivity for desmin, SMA, and S-100 protein was useful to exclude lesions with myofibroblastic components or differentiation such as myofibrosarcoma, nodular fasciitis, or fibromatosis. However, the histological sections of the recurrent tumor exhibited different features compared to the initial histological findings; it revealed increased multinucleated giant and atypical tumor cells and abnormal mitosis, and it was suggestive of malignancy. This case did not arise from the epithelial tissue but from the mesenchymal tissue of the breast, being consistent with the negative immunoreactivity for CK, EMA, SMA, desmin and S-100 protein. Histologic findings of many atypical cells and abnormal mitotic activity, a negative immunoreactivity for SMA and ALK helped to exclude IMT from the differential diagnostic consideration. This case was distinguished from myofibrosarcoma by negative immunoreactivity for SMA, CK, EMA, CD34, desmin and S100 protein. Although histological features of the recurrent mass were suggestive of a malignant pleomorphic spindle cell tumor, the immunohistochemical results failed to disclose the line of differentiation of the lesion. Hence, the final diagnosis of the tumor was undifferentiated pleomorphic sarcoma.

In conclusion, most breast cancers originate from the epithelium, and mesenchymal breast tumors are rarely seen, especially in men. Also, undifferentiated pleomorphic sarcoma, one subtype of primary breast sarcoma has been uncommon and these lesions represent special diagnostic difficulties. Herein, we reported a case of the undifferentiated pleomorphic sarcoma occurring in the male breast. Initially, it was difficult to classify the lesion as undifferentiated pleomorphic sarcoma; finally, based on histological findings and the immunohistochemical results of the tumor, we diagnosed the recurrent mass as undifferentiated pleomorphic sarcoma. In case of undifferentiated pleomorphic sarcoma of the breast, surgical excision of the tumor with adequate margins seems to be the most significant

prognostic factor; therefore, it will be necessary to treat this patient with repeated excision or simple mastectomy to prevent local recurrence and to improve his chances of survival.

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