Original Article

Rare Breast Malignancy Subtypes: A Cytological, Histological, and Immunohistochemical Correlation

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Abstract

Background: Breast malignancies encompass various subtypes which differ in their clinical presentations, outcomes, and response to the treatment regimens. Thus, a proper histological diagnosis and a special mention of the rare histologic subtypes are required to formulate clear recommendations of their treatment protocols. **Materials and Methods:** This is a 1-year retrospective study highlighting the rarely encountered subtypes on the mastectomy specimens received. **Results:** We encountered only 11 rare cases out of the total 153 mastectomy specimens received. The rare subtypes were as follows mucinous cystadenocarcinoma (0.6%), mucinous carcinoma (0.6%), dermatofibrosarcoma protuberans (0.6%), Squamous cell carcinoma (0.6%), papillary carcinoma (2.6%), medullary carcinoma (0.6%), and malignant mesenchymal tumor (1.3%). **Conclusion:** Our data suggest that these variants are distinct clinicopathological entities with a unique hormonal receptor status. Scant information is available on the rare breast tumor subtypes.

Keywords: *Cystadenocarcinoma dermatofibrosarcoma protuberans, malignant mesenchymal tumor, medullary carcinoma, papillary carcinoma*

Introduction

Invasive breast carcinomas are a group of malignant epithelial tumors characterized by invasion of the adjacent tissues and tendency to metastasis. The majority of these are adenocarcinomas derived from the terminal duct lobular unit.[1]

The WHO categorizes the breast tumors in 21 distinct histological types on the basis of cell morphology and architecture. Invasive ductal carcinoma (IDC) of no special type (ductal) is the most common type of invasive breast cancer accounting for approximately 65%–80% of the invasive breast neoplasms.[1-3] The invasive lobular carcinoma lags behind IDC (second most common) and accounts for only 5%–15% of the disease burden.[2-4] A widely accepted fact that the aggressive nature of the breast cancer can be determined by its histological type, grade, nodal status, and metastasis holds the ground even in the era of immunohistochemistry (IHC) and molecular pathology.[5,6]

The histological diversity of breast carcinomas has relevant prognostic implications as the management of breast tumors is a real challenge in the daily clinical practice.[6] The rare subtypes include other epithelial tumors such as tubular carcinomas (2%), medullary carcinomas (1%), papillary carcinoma, metaplastic carcinoma (<1%), and squamous cell carcinoma (SqCC) and other mesenchymal and stromal tumors/fibroepithelial tumors such as malignant lymphomas. The conventional paclitaxel-based neoadjuvant chemotherapy cannot be used in these variants; therefore, the accurate identification and diagnosis is required for the proper treatment of these patients.

Ethics

Ethical approval was obtained for this study. Informed consent was taken from every patient before the cytological procedure, mastectomy, histopathological examination, and IHC were carried out.

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Study design

This is a retrospective study in which the rare variants of breast tumors were highlighted using cytological, histopathological, and immunochemical techniques.

Materials and Methods

A 1-year study was conducted during the period of April 2017 to April 2018 on 153 mastectomy and lumpectomy specimens irrespective of the preoperative chemotherapy status. All the specimens were fixed in 10% formalin and were adequately grossed. The sections were stained using hematoxylin and eosin and were examined under a light microscope. IHC including estrogen receptor (ER), progesterone receptor (PR), HER2neu, and other markers was used, wherever necessary and applicable. The fine-needle aspiration slides of all the cases were reviewed retrospectively.

Results

The present study is a retrospective study of 153 cases. The patient's age ranged from 28 years to 85 years, and the mean was 52.9 ± 9.7 years. Of the total, 141 (92.1%) cases were reported as IDC. Only 11 (7.2%) cases were diagnosed as the rare histological variants of breast malignancy. These rare variants included papillary carcinoma (4), malignant mesenchymal tumor (2), mucinous carcinoma (1), mucinous cystadenocarcinoma (1), medullary carcinoma (1), SqCC (1), dermatofibrosarcoma protuberans (DFSP) (1). The details of these rare histological variants including the case summaries, fine-needle aspiration cytology (FNAC) findings, and histopathological and IHC findings are highlighted in Table 1. Herein, we are discussing all the important gross and histological features of the rare variants.

Mucinous cystadenocarcinoma

We received a mastectomy specimen measuring 12 cm × 10 cm × 6 cm with a mucinous grayish-white growth [Figure 1]. On microscopy, numerous dilated mucin-filled cystic spaces lined by tall columnar cells with abundant intra- and extracytoplasmic mucin, basally placed nuclei, and inconspicuous nucleoli were seen. The cells were CK-7 positive and CK-20, ER, PR, and HER2neu negative.

Table 1: Details of the rare cases highlighting cytology, histopathological, and immunohistochemistry findings

Case summary	Cytological diagnosis	Histopathological diagnosis	IHC
45 years/female, 2-cm × 2-cm lump in the upper outer quadrant of right breast	Pools of mucin	Mucinous cystadenocarcinoma	ER, PR, and HER2neu: Negative CK-7+ CK-20-
47 years/female, 4-cm × 3-cm lump in the upper inner quadrant of left breast	Hypocellular smears. Singly scattered spindle cells	Dermatofibrosarcoma protuberans	CD-34 strongly positive (4+)
49 years/female, 5-cm × 4-cm lump in the upper outer quadrant of right breast	Highly cellular smears. Poorly cohesive collections and singly scattered cells exhibiting marked pleomorphism and lymphocytic infiltrate	Medullary carcinoma	ER, PR, HER2neu, and S-100: Negative
43 years/female, 12-cm × 10-cm lump in the lower inner quadrant 28 years/female, 6-cm × 7-cm lump in the upper outer quadrant	Moderately cellular smears with many spindle cells exhibiting marked nuclear pleomorphism	Malignant mesenchymal tumor	Vimentin: Positive ER, PR, and HER2neu: Negative
38 years/female, 2 cm × 2 cm in the upper outer quadrant	Pools of mucin and few dyscohesive singly scattered cells	Mucinous carcinoma	ER, PR, and CK-7: Positive HER2neu: Negative
43 years/female, 15-cm × 14-cm lump right breast	Anucleate squames and squamous epithelial cells	Squamous cell carcinoma	CK5/6: Positive ER, PR, and HER2neu: Negative
56 years/female, 2-cm × 2-cm lump right side	Dyscohesive cell collections and papilleroid structures	Invasive papillary carcinoma	ER, PR: Positive HER2neu: Negative
40 years/female, 3.5-cm × 3-cm lump upper inner quadrant	Hypercellular smears with dyscohesive cell collections, ill-formed papillae	Invasive ductal carcinoma with invasive papillary carcinoma, comedocarcinoma, and cribriform pattern	ER, PR, and HER2neu: Negative
85 years/female, 3-cm × 2-cm lump left breast	Papillae with lining cells exhibiting marked nuclear atypia	Invasive papillary carcinoma	
55 years/female, 2-cm × 2-cm lump right breast	Dyscohesive collections of cells	Invasive papillary carcinoma	

IHC: Immunohistochemistry, ER: Estrogen receptor, PR: Progesterone receptor

Dermatofibrosarcoma protuberans

A 47-year-female presented to surgery outpatient department (OPD) with a breast lump for which mastectomy was done [Figure 2]. Serial sections through the specimen showed a grayish-white firm growth involving the overlying skin. On histopathological sections, a hypercellular tumor comprised monotonous oval-to-spindle cells resembling fibroblasts arranged in storiform pattern involving the dermis. On IHC, the cells were strongly positive for CD34 (4+).

Medullary carcinoma

A 49-year-old female presented to gynecology OPD with a 5 cm × 4 cm lump in the upper outer quadrant of the right breast. On serial slicing the mastectomy specimen, there was a large gray-white growth involving almost the entire breast. On microscopic examination, there were syncytial growth pattern, absence of gland formation, marked nuclear pleomorphism, and diffuse lymphoplasmacytic infiltrate. On IHC, the tumor was triple receptor negative and also negative for S-100 [Figure 3].

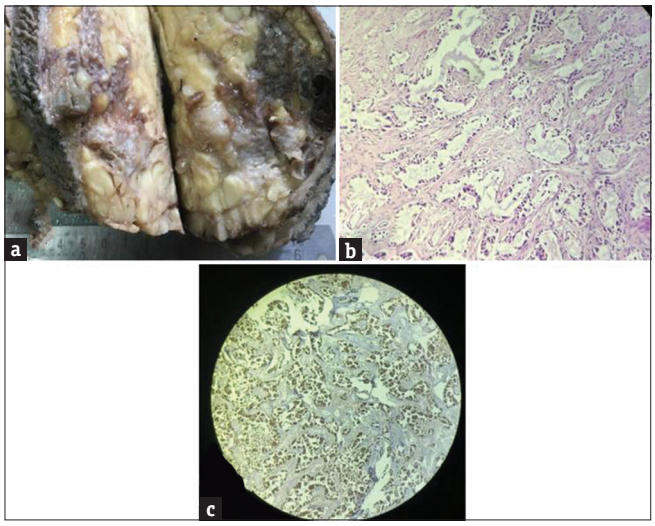

Figure 1: Mucinous cystadenocarcinoma (a) photomicrograph showing gross appearance (b) H and E (×400) (c) CK-7 + (×400)

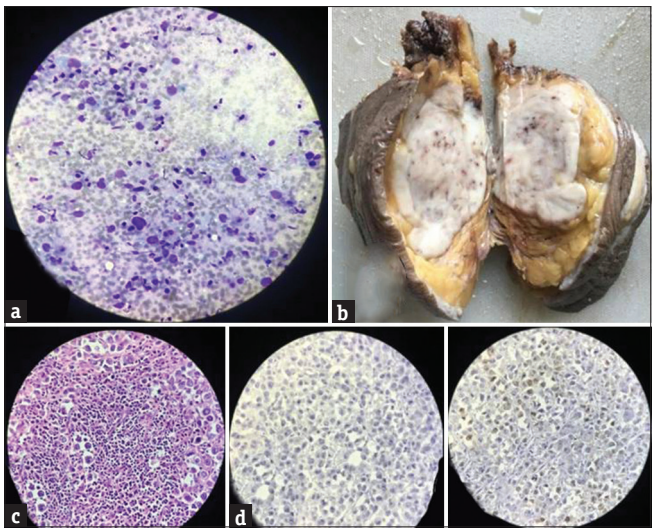

Figure 3: Medullary carcinoma (a) photomicrograph of fine-needle aspiration cytology smears May–Grunwald–Giemsa (×400) (b) gross examination of the mastectomy specimen (c) H and E sections (×400) (d) estrogen receptors, progesterone receptors-negative (×400)

Malignant mesenchymal tumor

Primary mesenchymal tumors are a rare malignancy of the breast. We encountered two female patients aged

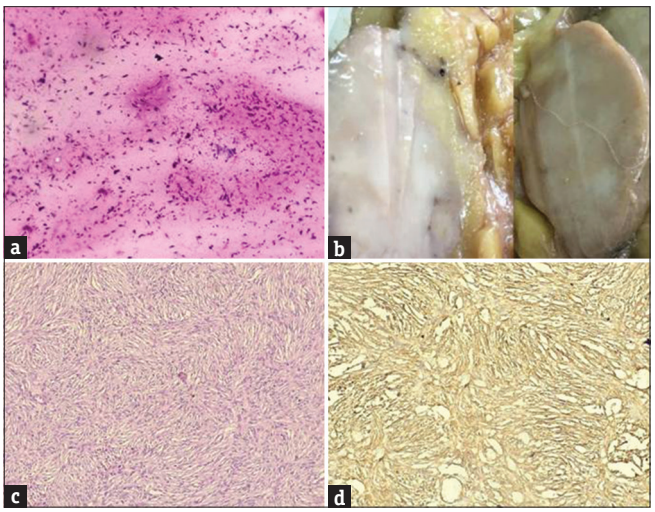

Figure 2: Dermatofibrosarcoma protuberans (a) photomicrograph showing fine-needle aspiration cytology smears May–Grunwald–Giemsa (×400) (b) gross appearance (c) H and E sections (×400) (d) CD-34 (4 +) (×400)

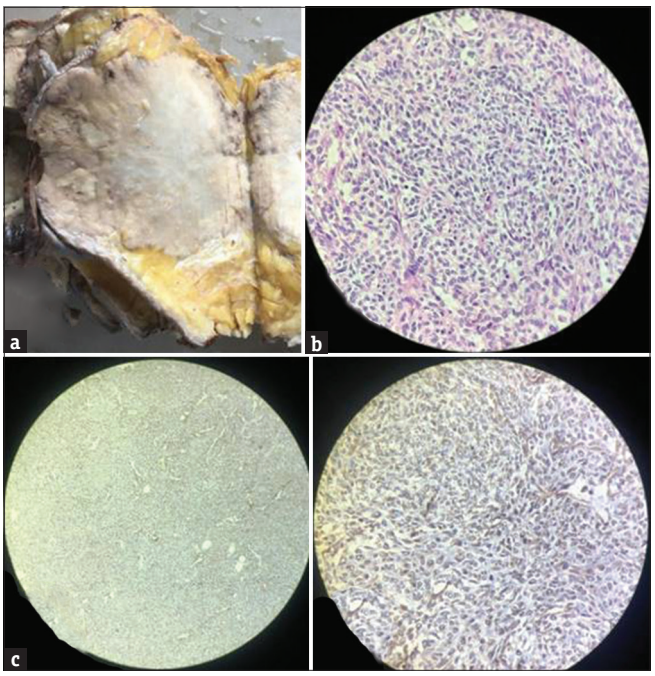

Figure 4: Malignant mesenchymal tumor (a) photomicrograph showing gross appearance (b) H and E sections (×400) (c) vimentin strongly positive (×400)

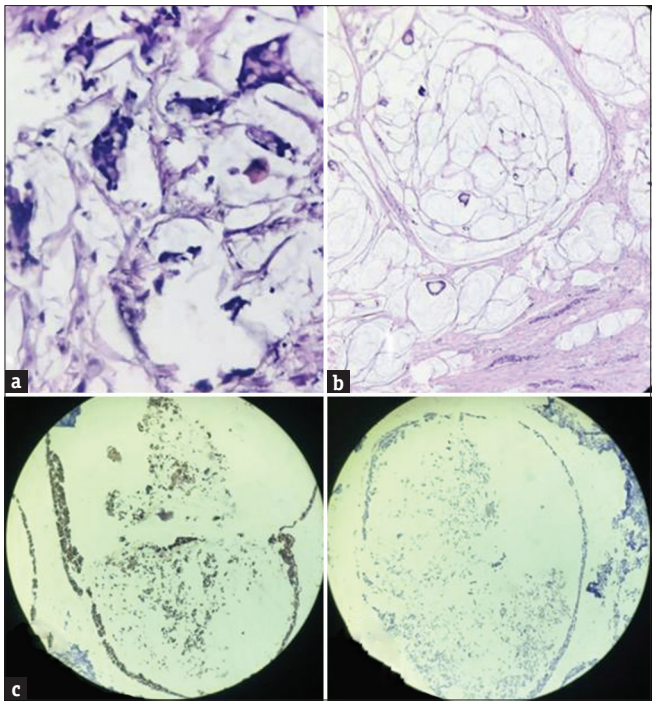

Figure 5: Mucinous carcinoma (a and b) photomicrograph showing H and E sections (×400) (c) CK-7 positive and CK-20 negative

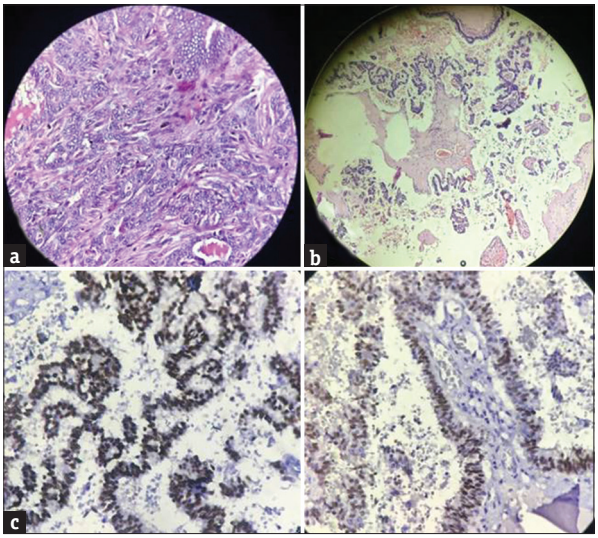

Figure 7: Papillary carcinoma (a) H and E sections (×400) showing both invasive ductal carcinoma and papillary (b) H and E sections from another patient showing invasive papillary carcinoma (×400) (c) Immunohistochemistry sections showing strongly positive estrogen receptors and weakly positive progesterone receptors

28 years and 47 years. On histopathology sections of both the patients, there were pleomorphic oval- and spindle-shaped cells exhibiting marked nuclear atypia, mitosis, atypical mitotic figures, and a background of necrosis [Figure 4]. The tumor cells were positive for vimentin and negative for S-100.

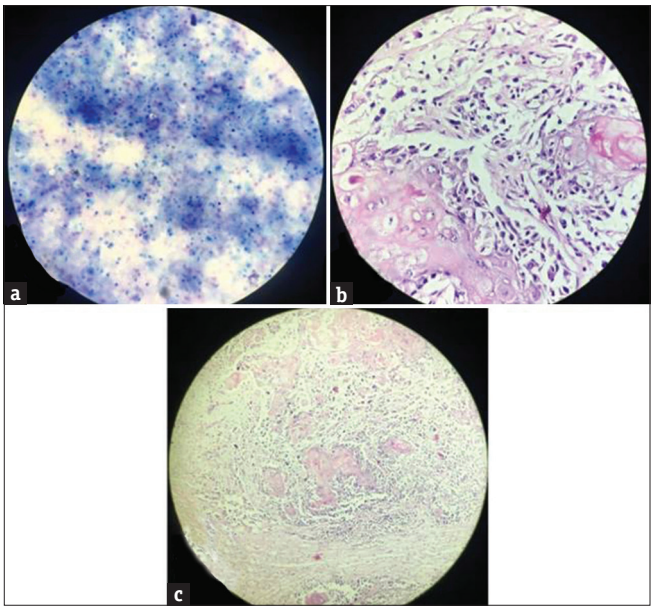

Figure 6: Squamous cell carcinoma (a) fine-needle aspiration cytology smears on May–Grunwald–Giemsa (×400) (b and c) H and E-stained sections showing keratin pearl formation

Mucinous carcinoma

A 38-year-old female presented with a lump which grossly was gelatinous in appearance with bosselated pushing margins. On histopathological examination, there were clusters of uniform round cells with minimal amount of eosinophilic cytoplasm floating in pools of mucin. These cells were positive for ER, PR, and CK-7 and negative for HER2neu and CK-20 [Figure 5].

Squamous cell carcinoma

We received a mastectomy specimen of a 43-year-old female with a 15-cm × 14-cm lump in the right breast. The tumor was involving the entire breast and causing ulceration of the overlying skin and nipple areola complex. On microscopy, the tumor was comprised >90% cells which were well-differentiated squamous cells. Extensive keratin pearl formation was also appreciated [Figure 6].

Papillary carcinoma

Over a period of 1 year, we encountered four cases of papillary carcinoma all of which were postmenopausal females. On microscopy, all the cases had well-formed papillae and absent myoepithelial cell layer. In one of the cases, we saw a mixed pattern, comprised IDC, extensive *in situ* carcinoma, comedocarcinoma, and invasive papillary component. Only one case was positive for ER, rest all were negative for ER, PR, and Her2neu [Figure 7].

Discussion

The rare and the special histological variants of breast malignancies often have a peculiar clinical behavior. However, considering the underlying fact that due to the rarity of these malignancies, the therapeutic regimen formulations are greatly affected. As a consequence, the clear treatment guidelines and recommendations are lacking for these variants.[3]

Herein, we are discussing the different types of breast malignancies which are rarely encountered on the day-to-day pathology practice.

Mucinous cystadenocarcinoma

An extremely rare variant of primary breast carcinoma belongs to the family of mucin-producing carcinoma sharing the same histology as the mucinous cystadenocarcinoma of the ovary and pancreas.[7-13] Similar to our case, most of these tumors are reported in postmenopausal females aged between 47 and 96 years.[7-13]

Dermatofibrosarcoma protuberans

DFSP is a mesenchymal neoplasm of the dermis and subcutis. It is a rare soft-tissue neoplasm, originally described in 1924 by Darier and Ferrand with a reported incidence of five cases per one million individuals per year.[14-16] This tumor rarely occurs in the breast and is the differential diagnosis includes other stromal tumors such as phyllodes tumor, pseudoangiomatous stromal hyperplasia, myofibroblastoma, leiomyoma, and periductal stromal sarcomas.

Medullary carcinoma

These represent <2% of breast carcinoma and occur frequently in the younger women. Despite their aggressive look, these have a good prognosis.[6,17]

Malignant mesenchymal tumor

Primary mesenchymal tumors/malignant tumors originating from mesenchymal tissue are rare malignancy of the breast. The metaplastic carcinomas which are characterized by a combination of mesenchymal and epithelial components are uncommon malignancies of the breast. Pure primary sarcomas are the rarest malignancies in mammary tissue. Few of the reported sarcomas include primary chondrosarcoma, spindle cell sarcoma, neuroectodermal tumor, and angiosarcoma.[18]

Mucinous carcinoma

Pure mucinous carcinomas (mucin component >90%) account for only about 2% of the breast carcinomas. Mucinous carcinoma of the breast is one of the rarer forms of intramammary cancer, often presenting as a lobulated, fairly well-circumscribed mass on mammography, sonography, and gadolinium-enhanced magnetic resonance imaging (MRI). It accounts for 1%–7% of all breast cancers and generally carries a better prognosis than other types of malignant breast cancers. Metastatic disease occurs at a lower frequency than in other types of invasive carcinoma. We present an atypical case of mucinous carcinoma in a woman who presented with a palpable intramammary lymph node metastasis from an unknown breast primary. Subsequent MRI and percutaneous biopsy demonstrated histologic findings consistent with a mixed mucinous neoplasm with a micropapillary pattern.

Invasive mucinous carcinoma of the breast is one of the rarer breast neoplasms and is typically associated with a better prognosis, a longer disease-free interval, and a lower incidence of axillary node metastasis. It often presents as a lobulated and/or well-circumscribed mass on mammography, sonography, and MRI.[1]

Squamous cell carcinoma

Pure primary SqCC of the breast is a rare (<0.1%) and aggressive tumor. It is considered to arise from metaplastic change of the ductal carcinoma cells.[19,20] This is a very aggressive, hormone receptor negative, and treatment refractory tumor with poor prognosis. The treatment of primary SqCC of the breast does not differ from other common histological types of breast cancer and may involve surgery, chemotherapy, hormonal therapy, and radiation therapy.

Papillary carcinoma

A rare variant of breast carcinoma comprises <2% of the breast malignancies.[21] It is predominantly seen in the postmenopausal women. Histologically, it is characterized by papillary lesion with absent myoepithelial cell layer.[21-23]

Conclusion

Due to the rarity of these tumors, there is an extreme paucity of literature in this area. Most of the literature available is in the form of case reports. Herein, we highlighted these rare diagnosis taking into consideration the cytological, histopathological, and immunohistochemical findings. Thus, a proper histological diagnosis and a special mention of the rare histologic subtypes are required to formulate clear recommendations of their treatment protocols.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts

will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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