



Original Article

A Study on Diversity of Malignant Breast Lesions in Urban Population of Bengal – Two Year Experience in A Tertiary Care Centre

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ABSTRACT

Background: Breast cancer is the leading cancer affecting females of urban India. In recent times the multidisciplinary approach to this cancer has given us new insights about its biology. New modalities of treatment and early diagnosis due to increased awareness have significantly reduced cancer related deaths. This study aims at portraying the morphological diversity of breast cancer and comparing with recent WHO (2012) classification. The multitude of histopathological variations of breast cancer intrigues us histopathologists not only from academic point of view but also helps us to guide clinicians regarding treatment and prognoses.

Material and Method: A cross sectional observational study conducted in the Department of Pathology from May 2015 to April 2017.

Result: Total 168 cases of breast carcinoma were diagnosed during this time period out of which maximum cases were clustered in the 5th decade of life. Most cases were stage T₂ and showed lymphovascular invasion. The special histopathological subtypes encountered were Pleomorphic IDC, Lobular Carcinoma, Cribriform Carcinoma, Medullary Carcinoma, Mucinous Carcinoma, Invasive Papillary Carcinoma, Micropapillary Carcinoma, Apocrine Carcinoma, Secretory Carcinoma, Stromal Sarcoma, Malignant Phyllodes and Primary Lymphoma of breast.

Keywords- carcinoma breast, WHO classification, rare histological subtype.

INTRODUCTION

Breast cancer has always dominated the accursed world of cancer since time immemorial. Procedures to remove breast tumors by cauterization were documented in Ancient Egypt dating back to hundreds of years BC. Presently in US 1 in 8 women develop breast cancer in the

course of her lifetime.¹ In India 1.5 lakh new cases of breast tumors amounting to >10% of all cancers have been diagnosed in 2016 as per ICMR.² It is one of the most comprehensively studied neoplasm not only histopathologically but also by immunohistochemical, molecular and genetic techniques. Despite of the fact that new

classification schemes have come up based on hormone receptor study, morphological classification still continues to remain the backbone of diagnosis by histopathologists. The adjuvant techniques have added advantage in determining treatment protocol but they are expensive and not available in all establishments especially in this part of the world. The most common type of breast cancer is Invasive carcinoma – no special type(IC-NST).³Well defined treatment protocol exists for IC-NST based on histopathological diagnosis and hormone receptor study however there exists a multitude of other breast tumors whose rarity of incidence made it impossible to study them thoroughly. Our knowledge about them is through case reports and review articles. This study was done to portray the diversity of breast tumors existing in this part of the globe. In this study we reviewed the data available and also shared our personal experience as histopathologists.

MATERIALS AND METHOD

This study was conducted in the Department of Pathology in collaboration with the Department of Surgery.

RESULTS

Table 1: Distribution of cases

S.No	Histopathological type	No. of cases	% age
1	IC-NST	143	85.11
2	Pleomorphic IDC	1	0.6
3	Lobular Carcinoma	1	0.6
4	Cribriform Carcinoma	1	0.6
5	Medullary Carcinoma	3	1.8
6	Mucinous Carcinoma	2	1.2
7	Invasive Papillary Carcinoma	2	1.2
8	Micropapillary Carcinoma	2	1.2
9	Apocrine Carcinoma	1	0.6
10	Secretory Carcinoma	1	0.6
11	Stromal Sarcoma	2	1.2
12	Malignant phyllodes	8	4.8
13	Primary Lymphoma of breast	1	0.6
TOTAL CASES		168	

Total number of cases were 168 out of which the predominant histopathological type of breast malignancy was Invasive carcinoma – no special subtype comprising 84.5% of total cases. This

Time period of this study was from May 2015 to April 2017.

The study was a cross sectional observational study.

Our study population comprised women of all age group whose mastectomy was done for malignant breast lesions. These women presented with chief complaint of lump in breast with or without nipple discharge. Initial investigations like mammography, FNAC or trucut biopsy were carried out and provisional diagnosis was made. Then modified radical mastectomy was done for the malignant tumors and the specimen was sent to us for histopathological confirmatory diagnosis. The specimen were grossed as per standard protocol and photographs were taken. After processing the tissue sections H&E staining was done and when required special staining like PAS or immunohistochemistry was done on the sections.

Ethical clearance and consent was taken for the cases.

finding was concurrent with existing data. Next commonest tumor was Malignant phyllodes tumor(4.8%).

Table 2: Distribution of cases as per age

AGE	NO.OF CASES	%age
<20	0	0
20-29	4	2.3
30-39	34	20.2
40-49	67	39.9
50-59	29	17.3
60-69	27	16
70 and above	7	4.2
TOTAL	168	

Maximum number of cases were in the age group of 40-49 yrs (39.9%) followed by 30-39 yrs (20.2%).

Table 3: Correlation of different histopathological subtypes with Bloom Richardson grading, lymphovascular and Perineural invasion, nodal metastasis and tumor size

HP DIAG	BR grade		LVSI		PNI		LN METS				TUMOR SIZE			
	2	3	Pos	neg	pos	neg	N0	N1	N2	N3	T1	T2	T3	T4
IC-NST(n=143)	124	19	98	45	7	136	70	34	26	13	31	76	27	9
Pleomorphic IDC(n=1)	-	1	1	-	-	1	-	-	1	-	-	-	-	1
Lobular Ca(n=1)	1	-	-	1	-	1	1	-	-	-	-	1	-	-
Cribriform Ca(n=1)	1	-	1	-	-	1	1	-	-	-	-	-	1	-
Medullary Ca(n=3)	-	3	1	2	-	3	-	0	2	1	-	-	2	1
Mucinous Ca(n=2)	2	-	-	2	-	2	2	-	-	-	1	1	-	-
Inv Papillary Ca(n=2)	2	-	1	1	-	2	-	2	-	-	-	1	1	-
Micropapillary Ca(n=2)	2	-	-	2	-	2	-	1	1	-	-	2	-	-
Apocrine Ca(n=1)	1	-	1	-	-	1	-	1	-	-	-	-	1	-
Secretory Ca(n=1)	1	-	1	-	-	1	-	1	-	-	-	1	-	-
Stromal Sarcoma(n=2)	-	-	-	-	-	-	2	-	-	-	-	-	1	1
Malignant phyllodes(n=8)	-	-	-	-	-	-	8	-	-	-	-	-	5	3
Primary Lymphoma of breast(n=1)	-	-	-	-	-	-	1	-	-	-	-	-	1	-

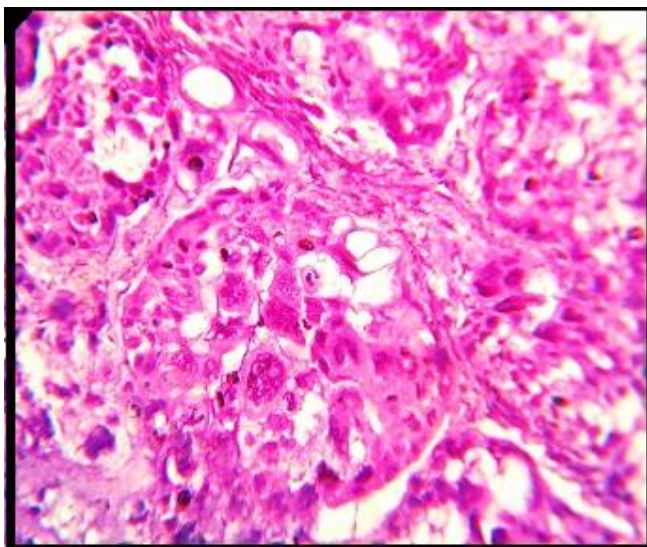


Figure 1: Microscopic picture of Pleomorphic IDC showing bizarre pleomorphic cells and giant cells.[H&E, 400X]

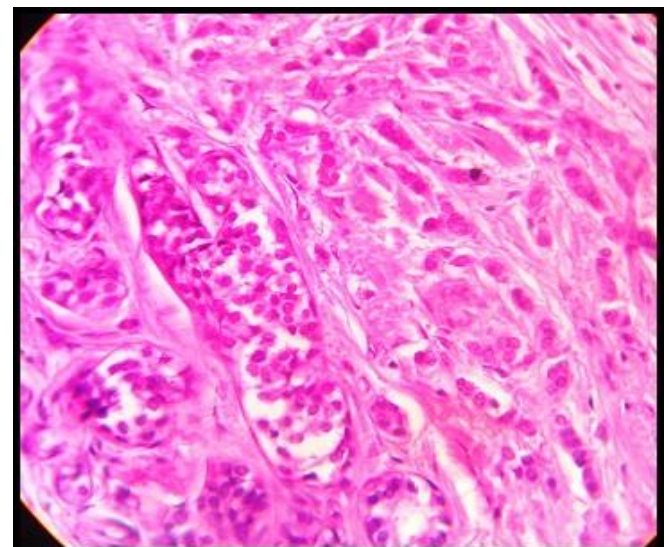


Figure 2: Microscopic picture of Invasive Lobular Carcinoma showing monomorphic cells in Indian file pattern and in situ lobular component. [H&E, 400X]

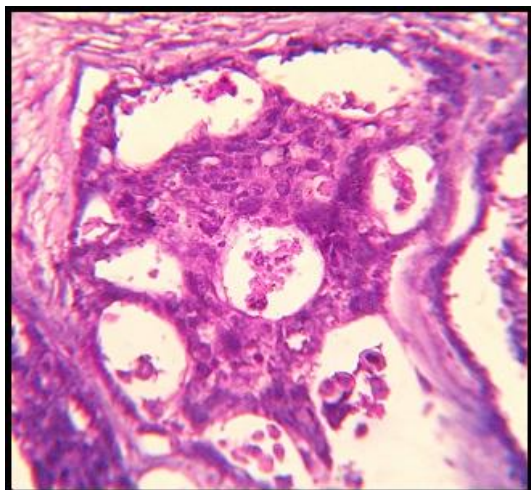


Figure 3: Microscopic picture of Invasive Cribriform carcinoma showing prominent cribriform architecture. [H&E, 400X]

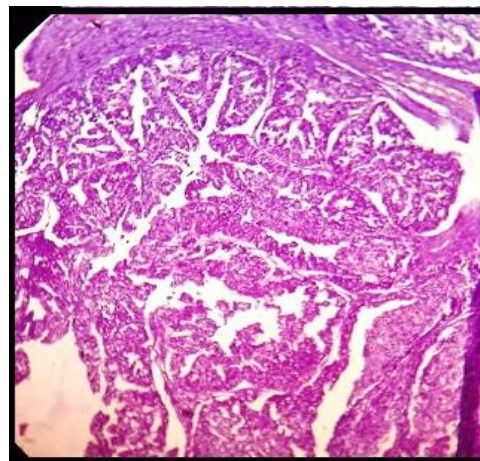


Figure 6: Microscopic picture of Invasive Papillary carcinoma showing well defined papillary architecture lined by malignant epithelial cells. [H&E, 100x]

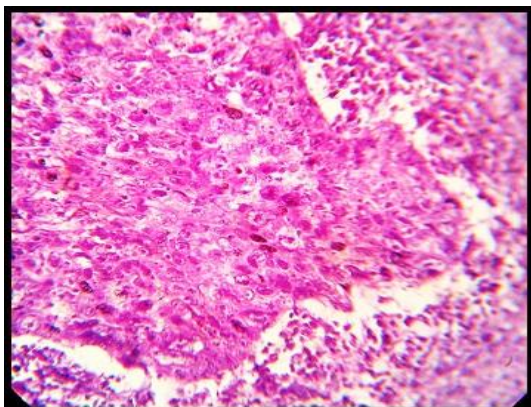


Figure 4: Microscopic picture of Medullary carcinoma showing syncytial island of cells with pushing margin and lymphocytic infiltrate. [H&E, 400X]

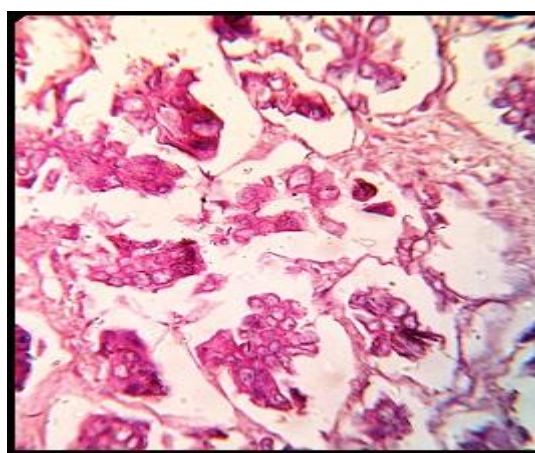


Figure 7: Microscopic picture of Micropapillary carcinoma showing small papilla in an empty space with tumor cells showing reverse polarity. [H&E, 400X]

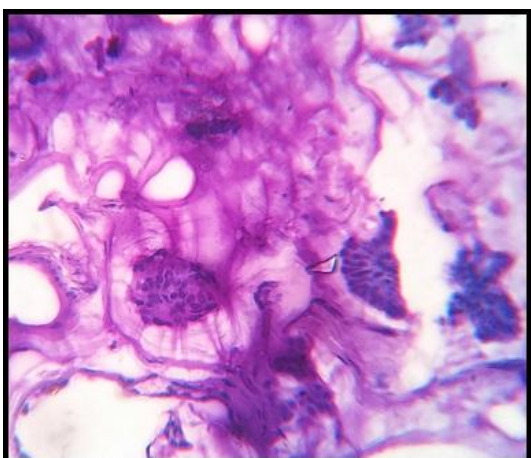


Figure 5: microscopic picture of Mucinous Carcinoma showing clusters of malignant cells with minimal pleomorphism floating in mucin. [H&E, 400X]

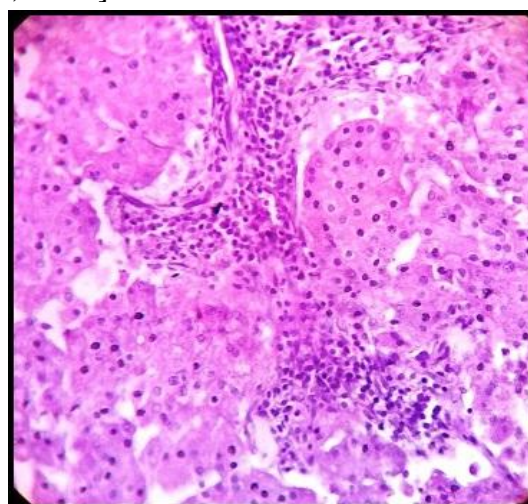


Figure 8: Microscopic picture of Apocrine carcinoma showing tumor cells with abundant granular eosinophilic cytoplasm. [H&E, 400X]

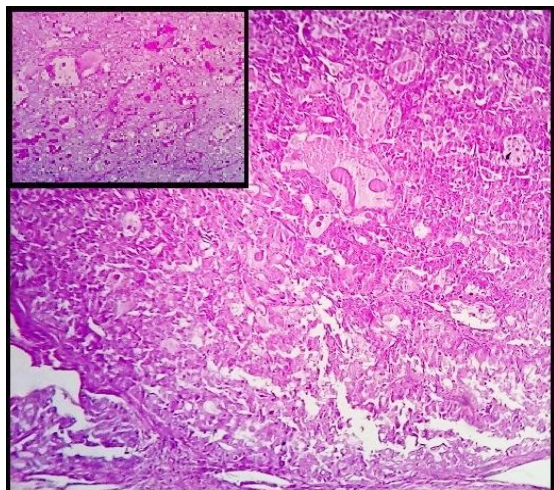


Figure 9: Microscopic picture of Secretory carcinoma with inset showing PAS positive secretions. [H&E, 400X]

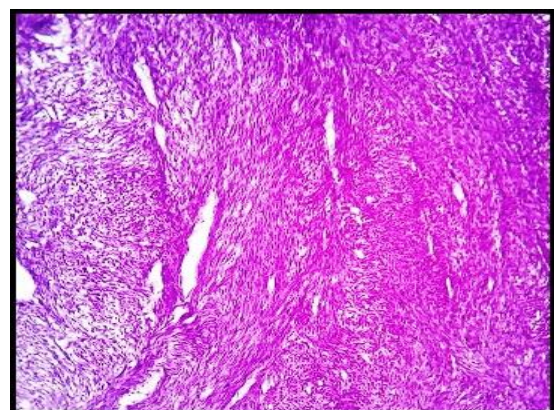


Figure 10: Microscopic picture of Stromal sarcoma with fibrosarcoma like features showing malignant stromal cells in herring bone pattern. [H&E, 100X]

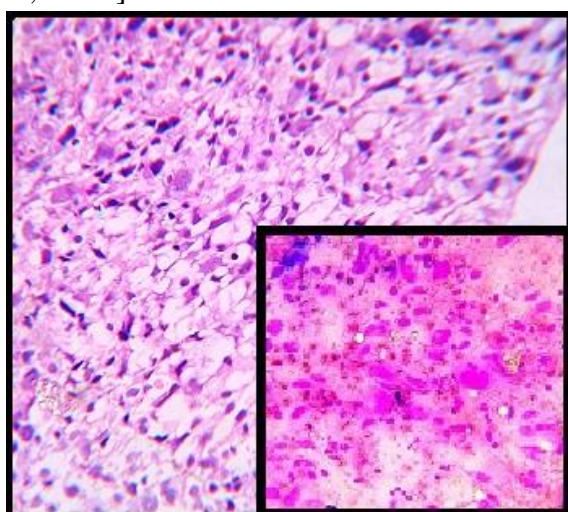


Figure 11: Microscopic picture of Stromal sarcoma with Rhabdomyosarcoma like features with inset showing prominent strap cells in the FNAC of same tumor. [H&E, 400X]

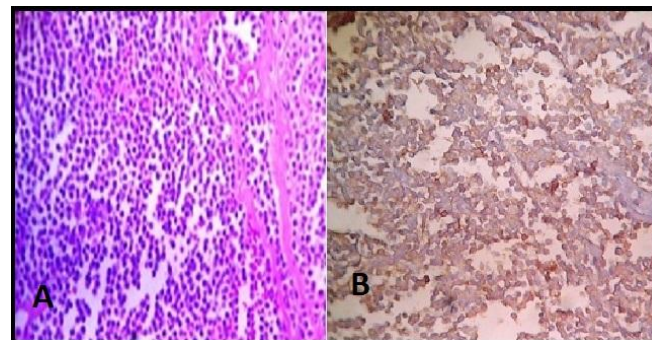


Figure 12: A-Microscopic picture of Primary Lymphoma of Breast showing atypical lymphocytes in sheets[H&E,100X]; B-Immunohistochemical staining with CD 20 show membranous positivity of all the lymphoid cells[IHC:CD20, 100X]

DISCUSSION

In this study the distribution of breast tumors were compared with age, grade, lymphovascular and Perineural invasion, lymph node status and tumor size. Majority of the breast malignancies were in the age group of 40-49 years (39.9%), followed by 20.2% in the age group of 30-39yrs. This finding corroborates with the population based ICMR cancer registry of India and the study of Albrektsen G et al.^[5,6] Majority of the tumors were Bloom Richardson Grade 2 (79.8%) corroborating with existing literature.^[6] Lymphovascular invasion was seen in 104 cases(61.9%) whereas Perineural invasion was relatively uncommon(4.2%). As per our findings the lymph node status in maximum patients were negative (50.6%) and the size of the tumor was less than 5 cm(68.5%).^[6] The increased consciousness among general population about breast cancer is the cause behind early diagnosis in lower clinical stages.

Next we describe the rarer tumors with special emphasis on their specific findings and also compare with the recent WHO (2012) criterias for diagnosis.

Pleomorphic IDC –

Pleomorphic IDC is a rare variant of invasive carcinoma – NST from which it is distinguished by presence of pleomorphic bizarre cells and multinucleate giant cells. This comprises >50% of

the tumor in the background of metaplastic spindle cells and squamous differentiation along with the adenocarcinoma. Age of presentation can be from 28 to 96yrs. Grossly it presents with large palpable mass. The tumor is typically BR grade 3 with high mitotic figure and central necrosis. ER/PR is typically negative and her2 overexpression may be seen. Prognosis of the tumor is poor.^[3]

Our case was a 49 yrs old lady with right breast tumor, T₂N₃M_x, BR grade 3 (figure 1)

Lobular carcinoma –

Invasive lobular carcinoma accounts for 5-15% of invasive breast tumors. Mean age of presentation is slightly higher than invasive carcinoma-NST. Clinically it appears as a ill defined palpable mass, sometimes multicentric. USG is more sensitive in detecting lobular carcinoma than mammography. Under the microscope classic lobular carcinoma is characterized by proliferation of small cells lacking cohesion and appearing individually dispersed through a fibrous connective tissue or invading the stroma in a single file. There is negligible host reaction or distortion of background architecture. Individual cells have round or notched ovoid nuclei and thin rim of cytoplasm. Mitosis is rare. Estrogen and progesterone receptors are positive and her2 over expression is not seen. The tumor cells show loss of E Cadherin expression.^[3,7]

We encountered just one case(0.6%) of lobular carcinoma insite of higher incidence worldwide. Grading of the tumor was T₂N₀M_x, BR grade 1. (Figure 2)

Cribriform carcinoma –

Invasive Cribriform carcinoma (ICC) accounts for 0.3-0.8% of breast carcinomas. It has a favourable outcome after treatment with 10 year survival between 90-100%.The mean age of diagnosis is 53-58 years. In mammography it is visible as a spiculated mass with microcalcification. Histopathological diagnosis of pure ICC is made when >90% of the tumor is composed of invasive cribriform component (sieve like spaces formed by arches of cells). Individual cells are small to

moderate in size with mild to moderate pleomorphism. Stroma is fibroblastic. The invasive component is often associated with cribriform DCIS. ICC is distinguished from cribriform DCIS by lack of myoepithelial layer. Mitoses is rare. This tumor falls in the molecular class Luminal A ie hormone receptor positive and lack of HER2 overexpression.^[3,8]

We came across this case of invasive cribriform carcinoma of left breast (Figure 3) in a 45yr old woman with left breast lump who was previously diagnosed ductal carcinoma in FNAC.

Medullary carcinoma –

As per the WHO 2012 new classification carcinoma with medullary features includes Medullary carcinomas, Atypical Medullary carcinoma and Invasive carcinoma-NST with medullary features. Prognostically these tumors have favorable outcome. Classical Medullary carcinoma(MC) is <1% of all breast carcinomas. The mean age of diagnosis is 45-52 years however another peak is noticed in <35yrs. Histopathologically to diagnose Medullary carcinoma the following 5 criterias must be met: 1) syncytial architecture in >75% of the tumor; 2) well circumscribed or pushing margin; 3) lack of tubular differentiation; 4) diffuse lymphoplasmacytic stromal infiltrate; 5) round tumor cells with abundant cytoplasm and pleomorphic high grade vesicular nucleus with several nucleoli. Frequent mitoses and atypical giant cells may be noted. Tumors which does not meet the above criteria are categorized under the other two groups atypical medullary carcinoma and IC-NST with medullary features. Medullary carcinoma is usually triple negative (ER/PR negative and no HER2 overexpression). BRCA1 germline mutation association has also been found.^[3,9]

We had 3 cases(1.8%) of Medullary carcinoma during our study period. First patient was 26yrs with a recurrence tumor (T₃N₁M_x, BR grade 3) (Figure 4) who had undergone 6 cycles of chemotherapy after previous lumpectomy operation. Second case was a 31 yr patient with

family history of breast cancer and third case a 51 yr woman who was diagnosed as Invasive carcinoma with medullary features.

Mucinous –

Pure mucinous carcinoma accounts for about 2% of breast carcinoma with increased incidence in elderly (>55yrs). Radiographically tumor appears as low density/hypoechoic well defined or microlobulated oval mass. Histopathologically it is classically described as nests of cells floating in lake of mucin. The nests are separated by delicate fibrous septa containing capillaries. Pure mucinous carcinoma show >90% mucinous differentiation and anything less is considered mixed type. Mucinous carcinoma can be divided into type A and type B. Type A is the classical variety containing large quantities of extracellular mucin whereas type B show larger cell clusters and frequent neuroendocrine differentiation. Individual cells have very minimal nuclear atypia. These tumors fall in the Luminal A molecular subtype and have excellent prognosis.^[3,10]

We diagnosed 2 cases (1.2%) of pure Mucinous carcinoma during our study period. One in an elderly 84yr old woman with bilateral breast carcinoma , one IC-NST and other one pure mucinous type(Figure 5). Other case was a 61yr patient(T₂N₀M_x)

Papillary –

Invasive papillary carcinoma is an invasive adenocarcinoma which has predominantly papillary morphology(>90%) in the invasive component. Very little information is available on this tumor due to rarity of incidence. Histopathologically the tumor consists of papilla lined by malignant epithelial cells with a fibrovascular core invading surrounding stroma. The main differential diagnosis is metastasis from papillary carcinoma at other sites. Data on prognosis is limited.^[3,11]

We came across two cases of Papillary carcinoma (1.2%) in the 2 year time period. One was present in a 40 year old woman another in a 47 year old woman. Both cases were considered primary since no other malignancy was detected.(Figure 6)

Micropapillary –

Pure micropapillary carcinoma is quite rare and accounts for only 0.9 to 2 % of invasive breast cancers. In mammography the tumor appears as an indistinct mass with micro calcifications. Histopathologically it is characterized by presence of hollow morula like aggregates of cuboidal to columnar malignant cells devoid of any fibrovascular core, separated from the stroma by an empty space which appears as lymphovascular invasion. Cytologically nuclear pleomorphism is minimal and cytoplasm is eosinophilic and either dense or finely granular. The neoplastic cells of micropapillary carcinoma exhibit reverse polarity (inside out) whereby the apical pole of neoplastic cells faces the stroma. These tumors are estrogen and progesterone receptor positive and Her2 results are conflicting. They also express MUC1. The prognosis of this cancer is not determined due to fewer number of reported cases.^[3,12]

Two cases of micropapillary carcinoma (1.2%), one in a 51 year old woman and another in a 35 year old woman were diagnosed during our study period. Both were low grade tumors with no nodal metastasis or lymphovascular or Perineural invasion. (Figure 7)

Apocrine carcinoma-

As per new WHO(2012) new nomenclature is Carcinoma with Apocrine differentiation. Focal apocrine differentiation is common in invasive carcinomas but extensive differentiation is seen in less than 4% of all breast carcinomas. Apocrine differentiation can be seen in other special types also like tubular, lobular, micropapillary and medullary. Individual cells have large nuclei prominent nucleoli and either abundant granular eosinophilic cytoplasm (type A) or abundant foamy cytoplasm (type B). Immunohistochemically these tumors demonstrate ER/PR negativity androgen receptor positivity and HER2 overexpression. These cells demonstrate GCDFP-15 positivity.^[3,13]

Our case diagnosed as apocrine carcinoma was in a 50 year old woman. The tumor was T₃N₁M_x, BR grade 2. (Figure 8)

Secretory carcinoma –

Secretory carcinoma accounts for less than 0.15% of all breast cancers. It is also called juvenile breast carcinoma and the median age of presentation is 25 yrs. Histopathologically secretory carcinoma show pushing border. Architecturally they present in microcystic, solid and tubular pattern. Microcystic pattern mimicks thyroid follicles. Luminal secretion is seen along with intra and extracellular secretions which are PAS and Alcian Blue positive. Cells are polygonal with granular eosinophilic foamy cytoplasm and nucleus are regular with inconspicuous nucleoli. This carcinoma is triple negative and EMA, alpha lactalbumin and S-100 are frequently expressed. These carcinomas are low grade and associated with favourable prognosis. However in older patients chance of recurrence is increased.^[3,14]

Our case was a 60 year old female with T₂N₁M₀, BR grade 2 tumor. The secretory material in the lumina were PAS positive. (Figure 9)

Malignant Phyllodes –

Phyllodes tumor of breast are fibroepithelial lesions derived from intralobular or periductal stroma. They are categorized as benign, borderline and malignant based on specific criteria. Malignant Phyllodes are rare tumors characterised histopathologically by marked nuclear pleomorphism of stromal cells, stromal overgrowth, absence of epithelial elements and increased mitoses(>10 per 10 HPF), increased stromal cellularity with diffuse infiltrative border. Heterologous elements may be present. Phyllodes tumor have high chance of recurrence and recurrent tumors have high chance of malignancy. Malignant phyllodes is seen in all age groups.^[3,15]

Malignant phyllodes tumor is relatively uncommon compared to its benign counterpart. We encountered 8 cases of malignant phyllodes tumor out of which 7 cases were in between 20-35 years age and one case was in a 43 years old woman. The tumors were mostly large destroying whole of breast tissue. The largest one we came across was 23cm in maximum dimension. Lymph nodal metastasis was absent in all cases.

Stromal Sarcoma –

We had 2 cases(1.2%) of stromal sarcoma in our study period. First case was a 45 yr old female with fungating mass over right breast. Histopathology showed Stromal sarcoma with Fibrosarcoma like features(Figure10). Another case was a 44 yr old woman with a large heterogenous SOL involving all quadrants of left breast. FNAC of the lesion followed by histopathology of the MRM specimen showed prominent strap cells along with other pleomorphic cells. So diagnosis of stromal sarcoma with rhabdosarcomatous differentiation with no nodal metastasis was made.(Figure 11).

Primary rhabdomyosarcoma of breast is exceedingly rare and seen in children mostly. Heterologous rhabdomyoblastic differentiation in malignant phyllodes or metaplastic carcinoma is more frequent in older women. True primary rhabdomyosarcoma is mostly of alveolar type. Pleomorphic type is seen in the heterologous component of malignant phyllodes. Breast involvement by metastatic rhabdomyosarcoma has poor outcome.^[3,16]

Lymphoma of Breast –

Primary breast lymphomas are rare with reported incidence of 0.04-0.53% of all breast malignancies. Accurate diagnosis is imperative for treatment. Most cases are treated with CHOP chemotherapy along with surgical excision.^[3,17] Exclusion of possibility of metastasis from other sites need to be done to diagnose primary breast lymphoma. Our case was provisionally diagnosed as malignant lymphoma of breast histopathologically and then IHC was done for confirmation. The B-cell markers were positive (CD 20 membrane positivity seen) whereas T-cell marker was negative.(Figure 12)

Invasive ductal carcinoma or Invasive carcinoma-NST(as per WHO 2013) and Lobular carcinoma have been studied in randomized trials to determine the optimal treatment approach including surgery, endocrine, and chemo or radiation therapy. In these types of tumors, the therapeutic approach is generally well defined.

However, the rarer histopathological types (2% of all breast cancer) have unique prognostic and clinical characteristics.^[18-20] Because of the rarity of these tumors, there is no consensus regarding optimal treatment and it is difficult to conduct large studies to define the optimal adjuvant treatment. Most cases have been treated with standard therapy as there are no data to indicate special protocols. The management of uncommon tumors is often controversial due to the lack of large single-institution studies or randomized trials to define optimal treatment.

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