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Special Histological Types of Breast Carcinoma- A Retrospective Study.

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ABSTRACT

Background: Breast cancer is a heterogeneous disease that encompasses several distinct entities with remarkably different characteristics. Histological type is the most important aspect of breast carcinoma characteristics. Histological type is associated with differences in epidemiology, diagnostic issues, clinical course & prognosis. Histological special types account for about 25% of breast cancer. Aim-The aim of this study is to identify the incidence and morphology of special types of breast cancers prevalent in our locality along with assessment of IHC status(ER,PR,Her2/neu)for better understanding of rare malignant tumors. **Methods:** This was aretrospective analysis of all special subtypes of breast cancers over a period of six years (July 2011-June 2017) in the department of Pathology ,VSSIMSAR,Burla,Odisha.Clinicopathological parameters and IHC status were reviewed in all cases. **Results:** All patients were females with median age of 51 years and undergone modified radical mastectomy. Out of total 448 cases of all breast carcinomas22 cases are of special histologic types.Medullary carcinoma was the most common type (7cases)(13.8%) followed by metaplastic carcinoma(5cases)(22.7%), lobular carcinoma 3(cases)(13.6%),apocrine carcinoma 3(13.6%)cases, papillary carcinoma2(9%)cases, one(4.5%)case each of mucinous carcinoma and sebaceous carcinoma. **Conclusion:** The identification of the special types has a significant utility in luminal breast cancers and should be considered in therapeutic algorithm.

Keywords: Breast cancer, IHC, special types.

INTRODUCTION

Breast carcinoma is the most common malignant tumor and the leading cause of deaths due to carcinoma in women.[1] In India, breast cancer is the second most common cancer (after cervical cancer).Breast cancer incidence increases rapidly after the age of 30.[2]

Histological type is one of very important characteristics of cancer. Histological type is associated with differences in epidemiology, diagnostic issues, clinical course, and prognosis. The World Health Organization (WHO) has presented a detailed classification of breast cancers.[3]

The 'histological special types' (HST) account for up to 25% of all breast carcinomas (BC), while the majority (50%–80%) of BC correspond to the invasive ductal carcinomas, not otherwise specified (IDC-NOS).[4]

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Estrogen and progesterone receptors are weak prognostic markers of outcome and strong predictive markers of response to endocrine (for example, tamoxifen-based) therapy,[5,6] and are the only immunohistochemistry(IHC)-based breast markers to have received the imprimatur of a consensus committee of the College of American Pathologists.[7] Estrogen receptors (ERs) expression has long been considered to be present in two-thirds of breast cancers[6], but more recent studies suggest that its incidence may be closer to 70%.[8]

Analysis of progesterone receptor (PR) expression is generally reported along with ER expression, and IHC determination of PR expression has now been clinically validated.[9]

HER-2/neu was one of the first oncogenes studied in samples of invasive breast cancer and it is identified in 10%-20% of breast cancer patients. It is a marker for sensitivity to Herceptin (trastuzumab), and resistance to Tamoxifen.[10]

The molecular subtypes of breast cancers include: Luminal (two sub-groups: ER-positive, HER2/neu negative with low proliferation and ER-positive, HER2/neu negative with high proliferation), HER2/neu positive and basal-like. These molecular groups predict clinical outcome and response to

therapy. Among these molecular subtypes, the basallike subtype has worst prognosis.[2]

Immunohistochemical classification:[11]

Subtype1= ER/PR positive, HER2/neu positive
Subtype2= ER/PR positive, HER2/neu negative
Subtype3= ER/PR negative, HER2/neu positive
Subtype4=ER/PR negative, HER2/neu negative This classification provides both therapeutic and prognostic information.

MATERIALS AND METHODS

A retrospective analysis of all resected breast carcinoma specimens from JULY 2011 to July 2016 was completed in the Department of Pathology,VSSIMSAR,Burla,Odisha. A total number of 448 cases were retrieved out of which 22 cases were diagnosed as special types of primary breast cancer and 426 cases were diagnosed as IDC-NOS types. Clinical data regarding age of the patient, tumor size, lymph node status and type of surgery were evaluated . The specimens were fixed in 10% neutral buffered formalin,paraffin sections were stained using conventional Hematoxyline& Eosin stains . All diagnosis were reviewed using the criteria of WHO classification 2012. Histologic grading by modified Bloom Richardson grading (Notingham Histologic Score) was given .IHC evaluations of ER,PR and Her 2 neuwas done on 10% neutral buffered formalin (NBF) fixed paraffin embedded tissue sections using Dako FLEX Ready to use mouse monoclonal Antibody (optimally diluted) and Dako Envision TM FLEX /HRP detection reagent [ER Clone EP1(Dako), PR Clone PgR 636(Dako), Anti-Her 2 / ErbB2 EP3(Bio jenex)].

RESULTS

During the study period, a total number of 448 cases of primary breast cancer were diagnosed out of which 22 cases of special types constituting 4.9 % . Carcinoma with medullary features 7 cases (31.8%) [Figure 1] was the largest group followed bymetaplastic carcinoma 5 cases (22.7%) [Figure 2], lobular carcinoma 3 cases (13.6%) [Figure 3], apocrine carcinoma 3 cases (13.6%) [Figure 4], papillary carcinoma 2 (9%) cases, 1 (4.5%) case each of mucinous carcinoma and sebaceous carcinoma [Figure 5] [Table 1]. All cases were female with median age of 51 years [Table 2]. All the tumors were unilateral. All the patient had undergone modified radical mastectomy .

According to TNM staging of breast cancer majority of the tumor belongs to stage II B (T2N1M0). 14 cases were with tumor size 2 to 5 cms(T2) and 16 cases were having N1 stage (<=3 lymphnode) with no clinical or radiological evidence of distant metastasis (M0). Out of total 22 cases , 4 cases were grade I, 12 cases were grade II and 6 cases were grade III. GradeII tumors were most frequently encountered followed by grade III tumor. Grade III tumors showed highest number of cases of lymph node involvement.[Table 2]

The routine application of immunohstochemical analysis for ER,PR and HER 2 status was carried out in all cases for scoring ER and PR Allred score was considered which include sum of proportion score and intensity score.

Proportion score was calculated% Positive as
Score 0=0% tumor cells
Score 1=1% tumor cells
Score 2=1-10% tumor cells
Score 3 =11-33% tumor cells
Score 4 = 34-66% tumor cells
Score 5 = 67-100% tumor cells

The intensity score for nuclear positivity of cells graded as
Score 1= none
Score 1= weak
Score 2 = moderate
Score 3 = strong

Total Allred score of 0-2 considered negative and 3-8 was considered positive.

Her2/neu was also reported with ASCO/CAP guidelines in which :

Score 0 (negative) no immunoreactivity or immunoreactivity in < 10% tumor cells.

Score 1+ (negative) faint/ weak immunoreactivity in >10% tumor cells and only portion of membrane positivity seen.

Score 2+ (equivocal) weak to moderate complete membrane immunoreactivity in >10% of tumor cells or complete, intense, circumferential membrane staining in ≤10% of invasive tumor cells.

Score 3+ (positive) complete, crisp, intense, circumferential membrane staining in >10% of invasive tumor cells (chicken wire pattern). ER, PR and Her2neu are categorized into molecular subtypes and correlated with Nottingham prognostic index.

Carcinoma with medullary features-Five cases were triple negative,two cases were ER-ve,PR-ve andHer2 +ve.

Metaplastic carcinoma-All five cases were triple negative.

Lobular carcinoma-Two cases were ER+ve, PR+ve, Her2+ve.One case wasER+ve,PR+ve, Her2-ve.

Apocrine carcinoma- One case was ER+ve, PR+ve, Her2-ve.Two cases were ER-ve,PR-ve,Her2+ve.

Papillary carcinoma-One case was ER+ve ,PR+ve, Her2+ve.One case wasER+ve,PR+ve,Her2-ve.

Mucinous carcinoma-One case was ER+ve, PR+ve, Her2+ve

DISCUSSION

Our study evaluates the morphology of special types of breast cancers along with assessment of luminal phenotypes.

Table 1: Histological Subtypes

Histological Types	No.of Cases
Medullary Carcinoma	7
Metaplastic Carcinoma	5
Lobular Carcinoma	3
Apocrine Carcinoma	3
PapillaryCarcinoma	2
Mucinous Carcinoma	1
Sebaceous Carcinoma	1
Total	22

Table 2: Clinical Variables

Sl No.	Variable	No. of Cases
1	Age	
	< 50 Years > 50 Years	9 13
2	Menopausal Status	
	Premenopausal Postmenopausal	08 14
3	Axillary Lymph Node	
	Negative Positive	15 07
4	Tumor Size (cm)	
	< 2 > 2	10 12
5	Tumor Grade	
	I II III	04 12 06

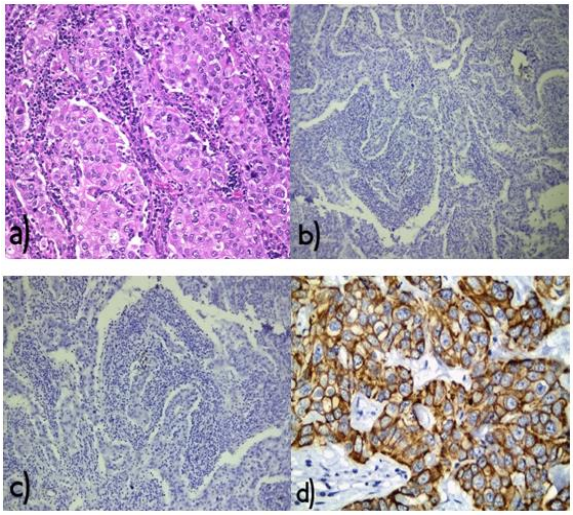

Figure 1: Medullary carcinoma: a)syncytial growth pattern, high grade nuclei and intense lymphoplasmacytoid infiltrate b)ER negative(ER IHC, 100X) c)PR negative(PR IHC,100X) d)Her2 positive 3+(Her2 IHC,100X).

Carcinoma with medullary features include medullary carcinoma (MC),atypical MC and a subset of invasive carcinoma of no special type (NST).These tumors demonstrates all or some of the following features: A circumscribed or pushing border, a syncytial growth pattern, cells with high grade nuclei, a prominent lymphoid infiltration.[12] Less than 5% of mammary carcinomas are medullary type in most series , but frequencies as high as 7% have been reported.[13] Inour study, out of 7 cases,3 cases were classic medullary carcinoma, 2 cases were atypical MC and one case was invasive carcinoma NST with medullary features. Medullary carcinaomas typically lack ER & PR expression as well as Her-2 amplification (triple negative) and show high proliferative and apoptotic activity.[14] Out of 7 cases , 5 cases in our study were triple negative.

Metaplastic breast carcinomas (MBC) represent a morphologically heterogeneous group of invasive breast cancer accounting for 0.2 to 5% of all invasive mammary carcinoma.[15] In our study, out of 448 cases of invasive breast cancer,5 cases (22.7%)were diagnosed as MBC. Out of five cases, two cases were squamous cell carcinomas, one case was high grade adenosquamous carcinoma, one case was spindle cell carcinomas and one case was metaplastic carcinoma with chondroid differentiation. Metaplastic carcinoma almost always do not express ER ,PR, or Her2 (triple negative),thus limiting potential systemic treatment.[14] All cases in our study were triple negative.

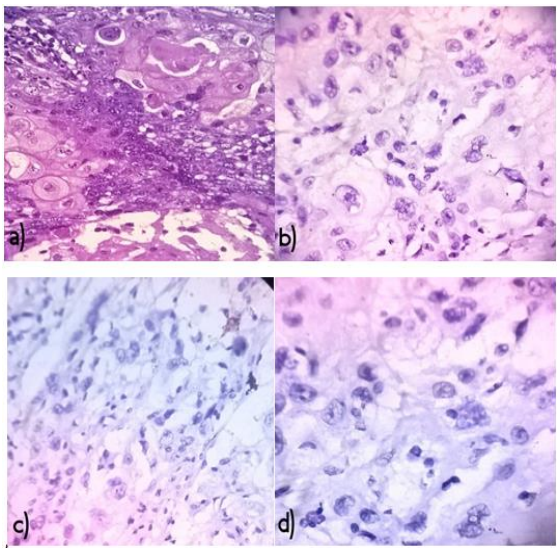

Figure 2 : Metaplastic carcinoma : a)nest of sqamous cells (H&E,400X) b) ER negative (IHC, DAB, 100X) c)PR negative (IHC, DAB, 100X) d)Her2 negative (IHC,DAB,400X)

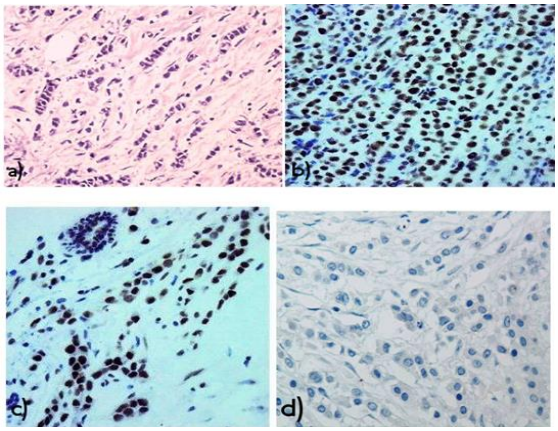

Figure 3: Lobular carcinoma,classic type : a) showing single files of tumor cells (H&E, 100X) b)ER positive (ER IHC, DAB, 100X) c)PR positive (PR IHC, DAB, 100X) d)Her2neu negative (Her2 IHC,100X).

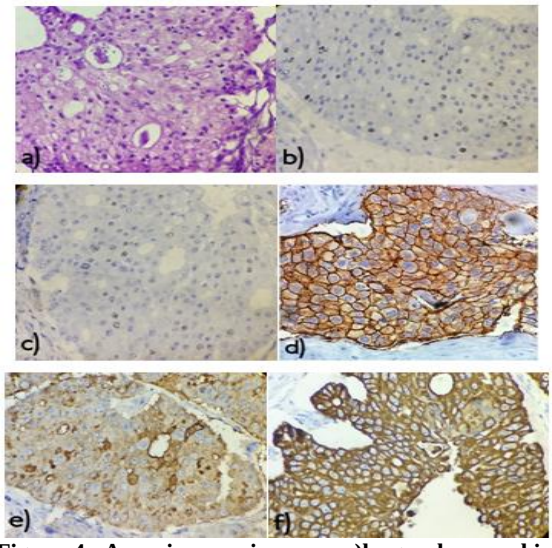

Figure 4: Apocrine carcinoma : a)large pleomorphic nuclei with prominent nucleoli & abundant granular eosinophillic cytoplasm (H&E,400X) b)ER negative (ER IHC, DAB, 100X) c) Prnegative (PRIHC, DAB,100X)d)Her23+strong membrane positivity (Her2 IHC, DAB.100X) e)GCDFP positive (IHC,DAB, 100X)d)ck positive (IHC, DAB, 100X).

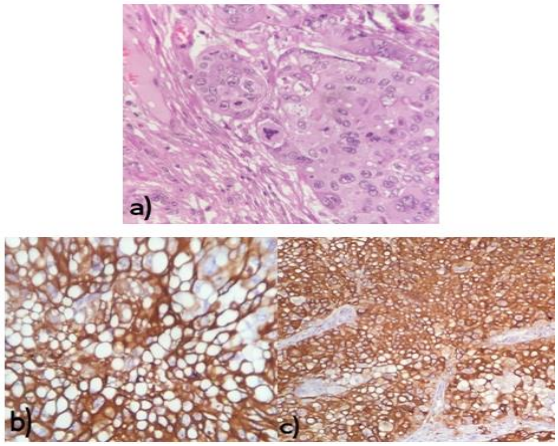

Figure 5: Sebaceous carcinoma : a) lobules of anaplastic pale clear cells& atypical mitosis (H&E, 400X) b)strong ck positivity (IHC, DAB, 400X) c)EMA positivity (IHC,DAB,100X).

Apocrine carcinomas are defined as showing cytologic and immunohistochemical features of apocrine cells in greater than 90% of the tumor cells .(15)Apocrine carcinoma constitutes fewer than 1% of breast cancer in most series.[14] The majority of intraductal and invasive apocrine carcinomas are negative for ER and PR.[13] Which is consistent with our study. In our cases, neoplastic cells have abundant granular, intensely eosinophilic cytoplasm. The cells are large with large pleomorphic irregular and hyperchromatic nucleus with prominent nucleolus .The prognosis of apocrine carcinoma, whether intraductal or invasive, is determined mainly by conventional prognostic factors such as grade, tumor size and nodal status.[14] Apocrine carcinomas tend to be immunoreactive for carcinoembryonic antigen(CEA).They are usually negative for s-100 protein and are always reactive for cytokeratin, GCDFP15 was detected in 55% of carcinomas including 75% of those with apocrine histologic features,70% of intraductal carcinomas, and 90% of infiltrating lobular carcinomas that had signet ring cell features.GCDFP15 mRNA detected by in situ hybridization is reported to be a more precise method for establishing apocrine differentiation than immunohistochemistry. Immunostaining for GCDFP15 has not been a useful predictor of prognosis.[13]

Mucinous carcinomas are relatively uncommon, accounting for between 1% and 4% of cases in asymptomatic series.[14] Microscopically the tumor consisted of small islands or clusters of cells consisting of uniform round epithelial cells set within extensive lake of extracellular mucin and having abundant granular, intensely eosinophilic cytoplasm. The cells are large with large pleomorpic irregular and hyperchromatic prominent nucleoli. Our case was positive for ER, PR and Her-2/neu. Pure mucinous carcinoma consistently express ER 100% and PR 70%, lack Her-2 expression (97%) and show a relatively low level of genetic instability.[14]

Invasive papillary carcinoma is a rare tumor occurring in fewer than 1% in most asymptomatic series.[14] In our cases there is presence of papillary structure with fibrovascular core showing invasion extending into mammary parenchyma and fat .The epithelial cells showed uneven stratification with loss of polarity, hyperchromatic nuclei with amphophillic cytoplasm .Mitotic figure was 3/10 HPF (40X) suggesting papilary carcinoma. Papilary carcinomas are usually estrogen and progestoron receptor rich and they tend to have a low growth rate when measured by thymidine labeling.[13] Both cases were ER and PR positive in our study.

Infiltrating Lobular Carcinoma is the most common special type of breast cancer accounting for 5% to 15% of cases. A classic subtypes accounts for approximately 40% of infiltrating lobular carcinomas. The majority of infiltrating lobular carcinoma are positive for ER (80%-95%) and (65%-75%) are positive for PR.[14] Our cases showed small discohesive cells dispersed individually and arranged in single files in fibrous tissue invading the stroma. The neoplastic cells had uniform round nuclei with inconspicuous nucleoli and a thin rim of cytoplasm. One case of alveolar variant showed globular aggregates of 20 cells. In our study, two cases were ER positive,PR positive and Her-2 positive. one case was ER positive,PR positive and Her-2 negative, consistent with other literatures.

Sebaceous carcinoma is a rare tumor accounting for 1 in 2000 cutaneous malignancies. Its most common site is face and is usually associated with Muir torre syndrome defined by sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma and

keratoacanthoma with sebaceous differentiation with at least one visceral malignancies.[16] To the best of our knowledge, our case is the second to be reported in literature of sebaceous carcinoma breast, a much rarer site for such a lesion after Pamela A. Propeck who reported a similar case associated with Muir torre syndrome in breast.[16] IHC markers like Androgen receptor,CK7, EMA and Adipophilin are usually done for confirmation.[17,18]

Microsection showed pleomorphic cells in sheets and nests. Individual cells are large having abundant foamy vacuolated cytoplasm with well defined outline, central to eccentric vesicular nucleus with irregular border and prominent nucleoli. Multiple cystic spaces were seen with eosinophilicsecretions, cells nests separated by fibrous septa with inflammatory cells and dilated blood vessels. Necrosis was present. Mitotic figure was 15/10HPF .Lymph node also showed carcinomatous deposits. With above features , a diagnosis of Malignant adnexal tumor (sebaceous carcinoma) of nipple areolar complex was made which needed further confirmation by IHC. The blocks were send outside the institute for confirmation on IHC due to lack of markers with us. Special stain like PAS was done which showed tumor cells as PAS negative.Two IHC markers were done to support the diagnosis on availability basis that comprised of CK7 and EMA. All the markers were positive in our case.

Sebaceous carcinoma of breast is included in WHO classification under primary breast carcinoma of skin adnexal type with sebaceous differentiation of at least 50% cells and there should be no evidence of cutaneous origin. It is a variant of invasive ductal carcinoma.[19] Our case had no invasive ductal component and no invasion in breast substance indicates it to be from cutaneous origin and it is therefore not a primary sebaceous tumor of breast. Microscopically shows sheets or lobules of atypical pale or clear cells with vacuolated cytoplasm.It usually affects ages 43 to 83 yrs.size ranges from 7.5 to 20cm.commonly associated with Muir torre syndrome. Sebaceous carcinoma may precede internal malignancy.

As lipids are washed out during processing it is not possible to perform lipid stains on paraffin sections. Intracytoplasmic lipid can be easily demonstrated on frozen section. Other method to demonstrate lipid is by immunostains. These tumors are also positive for adipophilin and have high Ki67 of 16% to 68%.Also they stains positive for ER,PR, androgen and HER2/neu. Also they are positive for Androgen receptor,EMA and CK7.[17,18]

Not much is known about prognosis. Sebaceous carcinoma are felt to have worst prognosis of all other cutaneous carcinomas. Due to scant published data, it is difficult to compare it with other breast carcinomas.[20]

It is important to differentiate primary sebaceous carcinoma breast from sebaceous carcinoma originating in skin of nipple areola as the former have an aggressive behavior and appropriate treatment is needed in former.

CONCLUSION

The present study indicate that an accurate and reliable histopathologic assessment is crucial in order to detect special types of cancer with particular regard to the need for adjuvant systemic treatment .In the current era of molecular medicine, the traditional biomarkers(ER,PR,Her2/neu)drive patient care and there is evidence linking these biomarkers to clinical outcome. Although a gene study is a sensitive technique, it lacks specificity in distinguishing different cells, may be contaminated by other cells. In addition, gene profile analysis is complex and inconvenient for routine clinical use. Future research would be aimed at identifying biomarkers specifically linked to histological subtypes of breast cancer.

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