IMMUNOHISTOCHEMISTRY AS SURROGATE MARKER FOR MOLECULAR TYPING OF SPECIAL TYPES OF BREAST CARCINOMAS

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ABSTRACT

BACKGROUND

Breast cancer is a heterogeneous disease with variable morphological features, clinical outcomes and response to different therapeutic options. Gene expression profiling studies on breast carcinomas have revolutionised the classification of breast carcinomas into molecular subtypes enhancing the treatment protocols and offering better prediction of outcomes.

MATERIALS AND METHODS

The present study aims to discuss the special histological variants with special emphasis on their molecular phenotype using surrogate immunohistochemical markers.

RESULTS

Special variants of breast carcinomas diagnosed during the study period of two years from August 2013 and July 2015 were classified into molecular subtypes using immunohistochemical expression of ER, PR and HER-2.

CONCLUSIONS

Special types of breast carcinomas are very rare and have different clinicopathologic behaviours. It is important to know their characteristics to make proper management decisions and to predict the prognosis.

KEYWORDS

IHC, Molecular Typing of Breast Carcinomas, Special Types of Breast Cancers.

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BACKGROUND

Breast cancer is the most commonly diagnosed malignancy in women worldwide and in India it ranks second to cervical cancer.[1,2] Epithelial breast cancers are a heterogeneous group of malignancies with different clinical behaviours, pathogenesis and prognosis.[3] According to the fourth edition of World Health Organization (WHO) classification, breast cancer can be classified into 21 distinct histological types on the basis of cell morphology, growth and architecture patterns.[4]

Most common type of breast cancer is invasive carcinoma of No Special Type (NST). This group comprises 40 to 75% of breast carcinoma cases. The diagnosis of this is made by exclusion of recognised specific types of breast cancers.[3] There are more than a dozen morphologically distinct special variants of breast carcinoma, which account for 25% of breast carcinomas, but still very well-defined by the WHO classification.[3] The fourth edition WHO classification proposed strict diagnostic requirements for special breast tumour types with their characteristic features being present in >90% of the tumour. Breast carcinomas that have a specialised pattern in at least 50% of the tumour and a non-specialised pattern in between 10% and 49% are designated as mixed invasive NST.[4]

The special histologic types of breast carcinoma are associated with specific genetic characteristics and clinical behaviours, which have prognostic significance.[5] The rare breast cancer group have different prognosis ranging from the tubular carcinoma, which is associated with an indolent clinical course to metaplastic cancer, which has unfavourable outcome.[3]

Based on gene expression profiling studies, breast carcinomas have been classified into intrinsic molecular subtype's luminal A and B, HER-2 and basal like tumours. In areas where gene expression profiling is not feasible, surrogate classifications based on Immunohistochemistry (IHC) have been proposed.[6] The expert panel of the St. Gallen in 2013 proposed to classify tumours for therapeutic purposes based on such "surrogate intrinsic subtypes."[7]

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AIMS AND OBJECTIVES

The aim of the present study is to discuss the rare histological variants of breast carcinoma encountered at a tertiary care center with review of literature.

To describe the epidemiology, clinical and immunohistochemical features of special epithelial breast tumours. The study also aims to apply the IHC profile as surrogate markers for molecular subtyping of breast carcinoma with special reference to rare histologic variants.

MATERIALS AND METHODS

This was a prospective study done in Upgraded Department of Pathology, Osmania General Hospital, for a period of two years from August 2013 to July 2015. All the cases diagnosed as duct cell carcinoma on both radical mastectomy or lumpectomy specimens were included in our study. All male breast carcinoma cases were excluded from our study.

The histopathological sections were routinely processed, stained with H and E. Immunohistochemistry was performed in all cases for Oestrogen Receptor (ER), Progesterone Receptor (PR), HER-2/neu.

RESULTS

During this period of two years, a total of 78 breast carcinoma cases were diagnosed in our hospital. Of these 61 (78.2%) were of IDC NST type, four cases were of lobular breast carcinoma and 13 (16.6%) cases were special or rare types of breast carcinomas.

Of the 13 rare types of breast carcinomas, 4 (5.1%) were papillary breast carcinomas, 4 (5.1%) cases were of metaplastic carcinoma, 2 (2.5%) cases of mucinous carcinoma of breast, 2 (2.5%) cases of medullary carcinoma of breast, one (1.2%) case of adenoid cystic carcinoma of breast.

Type	IDCC	Lobular ca.	Other Special Types
No. of case	61	4	13

Table 1. Showing Total Number of Cases of IDCC and Other Special Types

	Papillary Carcinoma (5.1%)	Metaplastic Carcinoma (5.1%)	Mucinous Carcinoma (2.5%)	Medullary Carcinoma (2.5%)	Adenoid Cystic Carcinoma (1.2%)
Mean age in years	54	50	58.5	48	68
Clinical presentation	Painless palpable lump	Painless palpable lump	Painless palpable lump	Painless palpable lump	Painless palpable lump
Laterality right left	 2 2	 2 2	 1 1	 1 1	 1

Table 2. Demographic Features

Gross Features	Papillary Carcinoma (5.1%)	Metaplastic Carcinoma (5.1%)	Mucinous Carcinoma (2.5%)	Medullary Carcinoma (2.5%)	Adenoid Cystic Carcinoma (1.2%)
Gross	Well-circumscribed g/w mass	Well-defined g/w solid nodular mass	Variegated with solid, cystic, areas with mucin	Well-circumscribed g/w mass	Well-circumscribed g/w mass
Size <2 cm			1		
2-4.9 cm	3	2		1	
>5 cm	1	2	1	1	1

Table 3. Gross Morphologic Features

	Papillary Carcinoma (5.1%)	Metaplastic Carcinoma (5.1%)	Mucinous Carcinoma (2.5%)	Medullary Carcinoma (2.5%)	Adenoid Cystic Carcinoma (1.2%)
Microscopic feature	Papillary fronds with prominent fibrovascular core	Pleomorphic spindle cells in fascicles, storiform pattern along with islands and nests of IDC	Small islands of cells in lakes of extracellular mucin	Syncytial growth pattern with lymphocytic infiltrate	Cribriform, glandular lumina and basement membrane like material
Bloom-Richardson Score	5 (Gr. I)	8 (Gr. III)	6 (Gr. II)	-	5 (Gr. I)
	5 (Gr. I)	7 (Gr. II)			
	4 (Gr. I)	9 (Gr. III)	6 (Gr. II)		
	3 (Gr. I)				
LN status Negative	4	2	1	1	1
Positive		2	1	1	

Table 4. Microscopic Features

Immunohistochemistry staining was done to look for expression of ER, PR and HER-2/neu. The immunohistochemistry results were used to classify the breast carcinomas into intrinsic molecular subtypes. 44% of the IDC NST type breast carcinomas belonged to luminal subtype. Special types of breast carcinoma fell into following subtypes.

	Molecular Subtype
Papillary carcinoma (n-4) (100%)	Luminal (ER+, PR+, HER-2-)
Metaplastic carcinoma (n-4) (100%)	Basal like (ER-, PR-, HER-2-)
Mucinous carcinoma (n-2) (100%)	Luminal (ER+, PR+, HER-2+)
Medullary carcinoma (n-2) (50%) (50%)	HER-2 (ER-, PR-, HER-2+)
	Basal like (ER-, PR-, HER-2-)
Adenoid cystic carcinoma (n-1) (100%)	Basal like (ER-, PR-, HER-2-)

Table 5. Immunohistochemistry Results

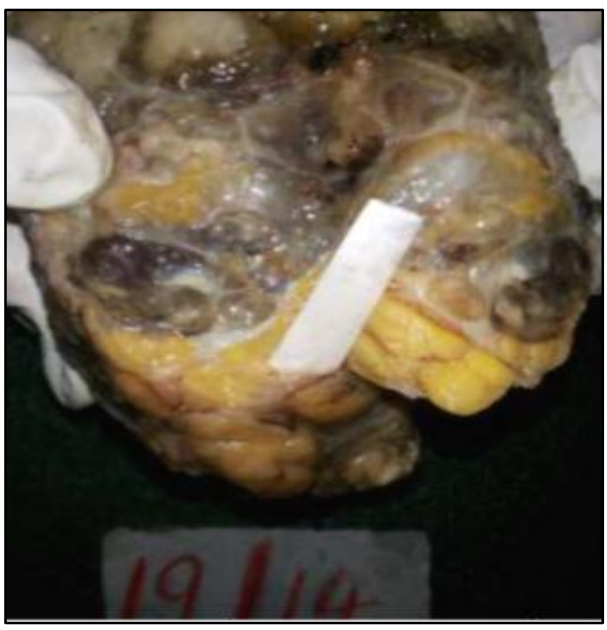

Figure 1. Gross Picture of Mucinous Carcinoma showing Variegated Appearance with Solid, Haemorrhagic and Cystic Areas Filled with Mucin

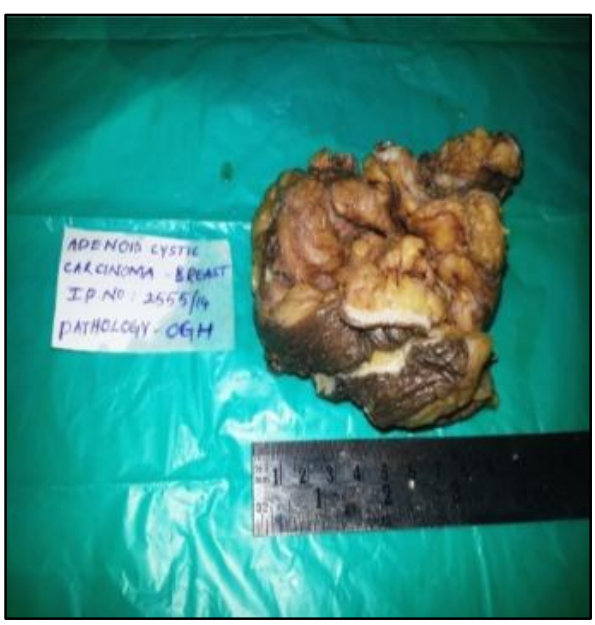

Figure 2. Gross Picture of Adenoid Cystic Carcinoma showing Grey White Mass with Cystic Space

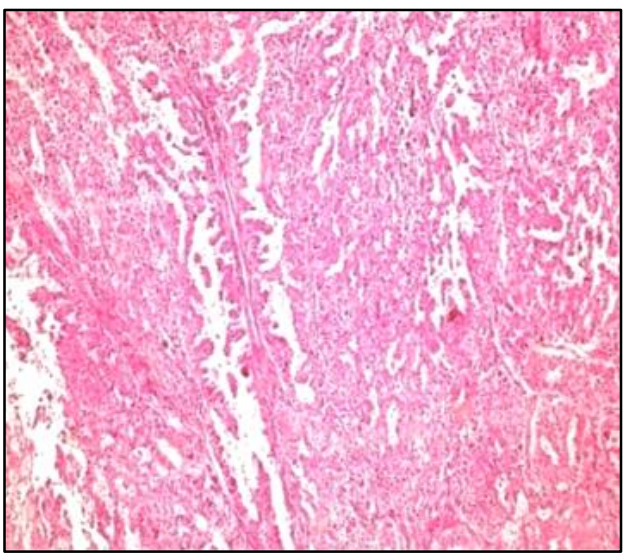

Figure 3. H and E Stained Microphotograph of Papillary Carcinoma showing Papillary Fronds with a Fibrovascular Core

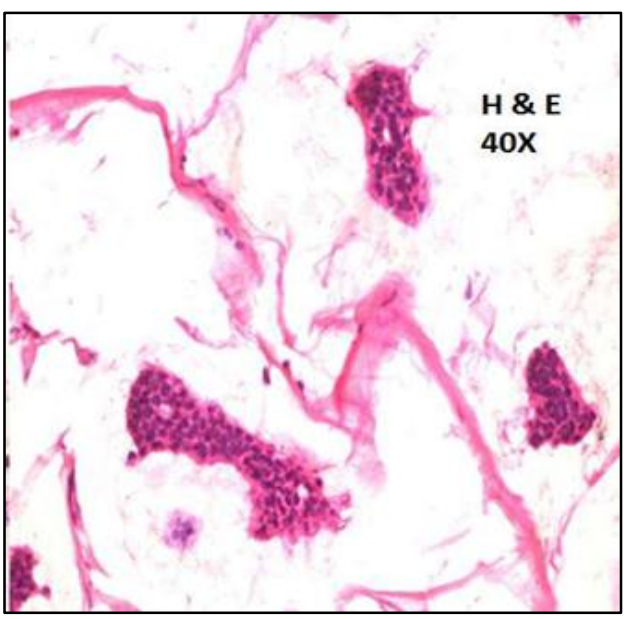

Figure 4. Mucinous Carcinoma H and E showing Islands of Tumour Cells Floating in Pools of Mucin

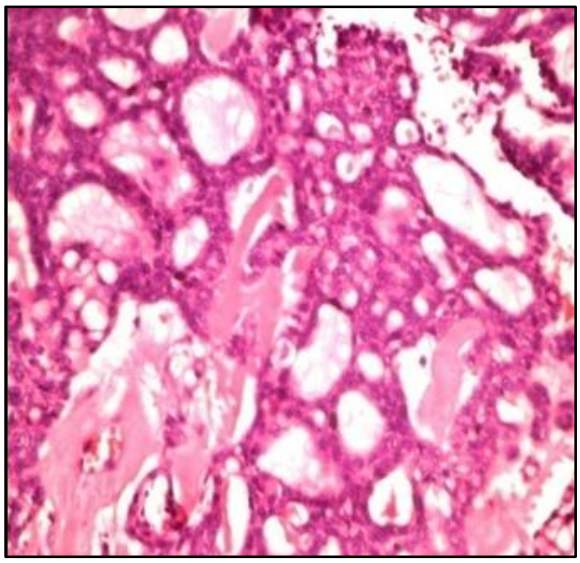

Figure 5. Adenoid Cystic Carcinoma showing Glandular Elements in Cribriform Pattern and Basement Membrane like Material

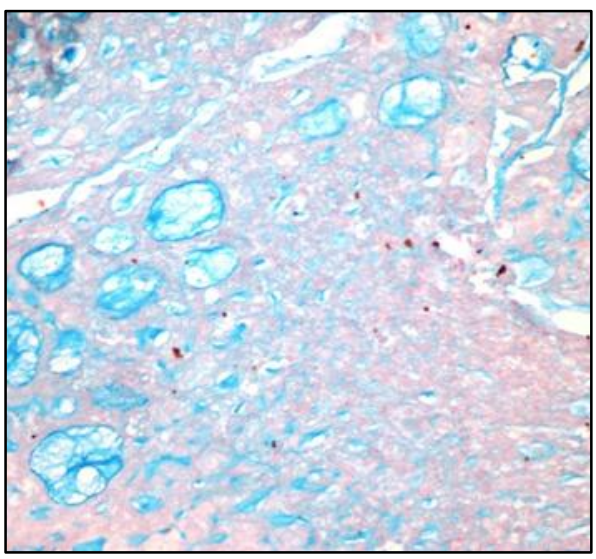

Figure 6. Adenoid Cystic Carcinoma Positive for Alcian Blue Staining

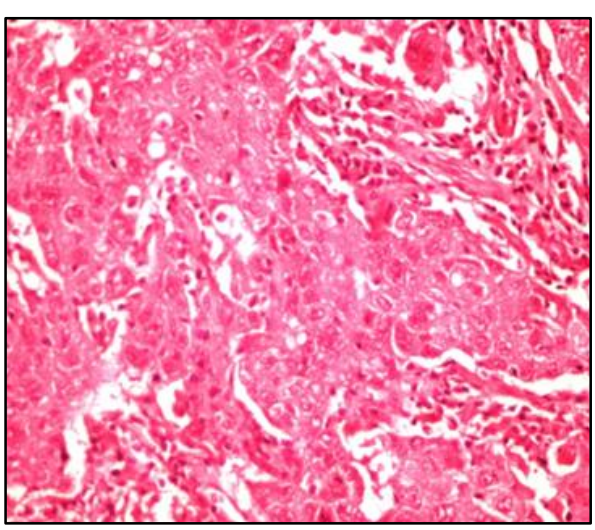

Figure 7. Medullary Carcinoma showing Syncytial Pattern of Arrangement of Cells with Lymphocytic Infiltrate

IHC IMAGES
Figure 8, 9, 10, 11 Showing IHC Images of Metaplastic Carcinoma

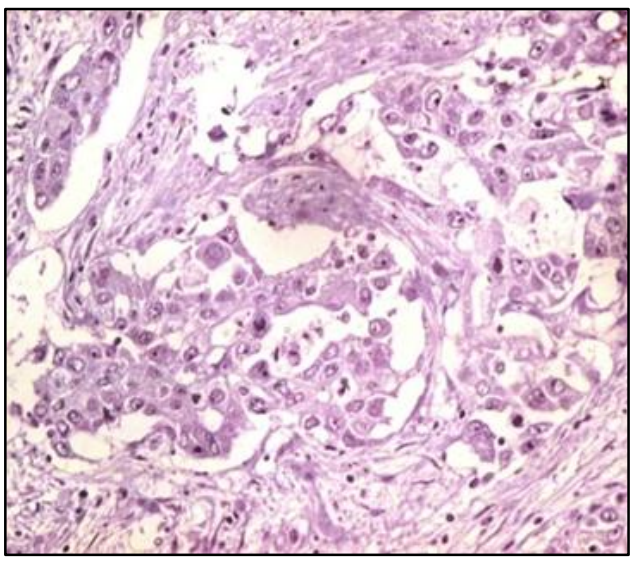

Figure 8. ER Negative

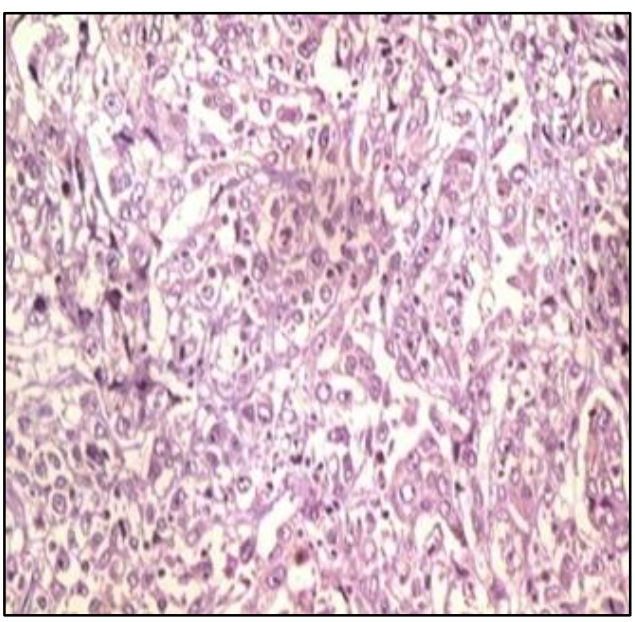

Figure 9. PR Negative

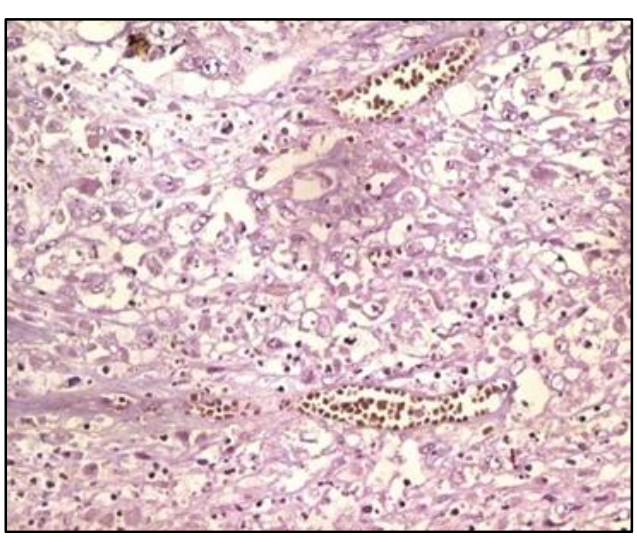

Figure 10. Her-2 Negative

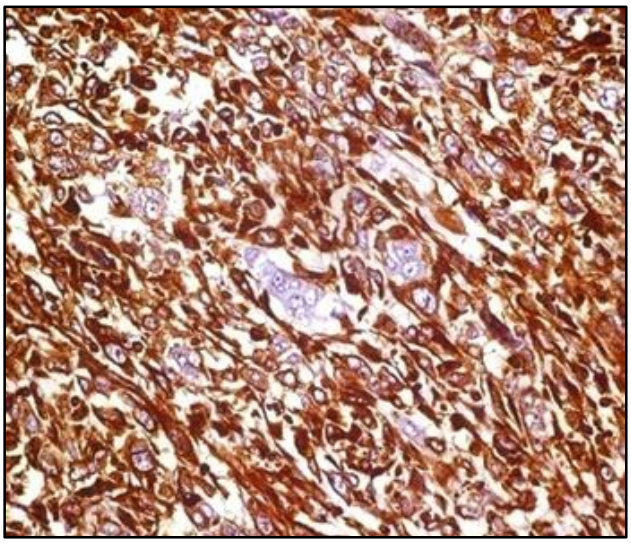

Figure 11. Vimentin Positive

Figure 12, 13 showing IHC Images of Mucinous Carcinoma

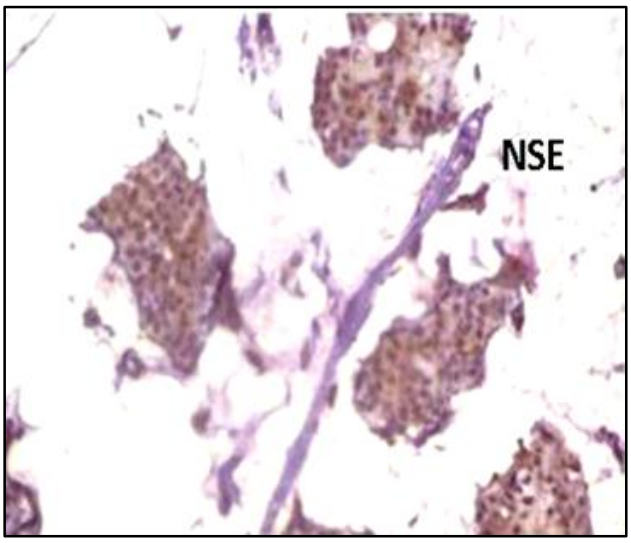

Figure 12. NSE Positive

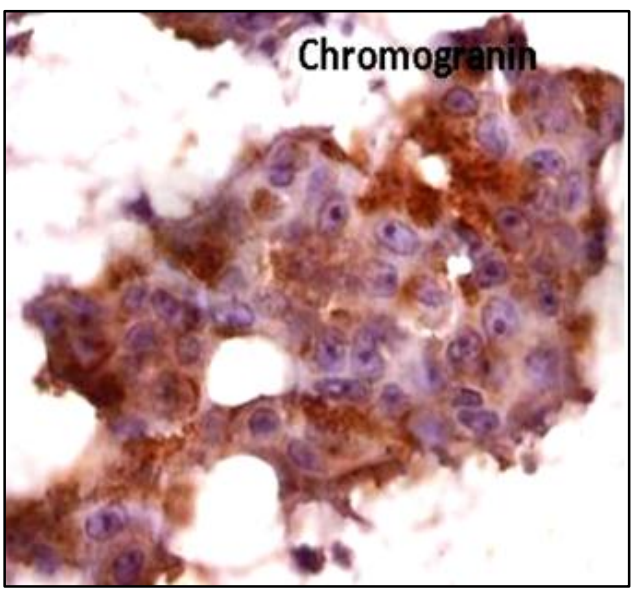

Figure 13. Chromogranin Positive

Figure 14, 15, 16- Showing IHC Images of Adenoid Cystic Carcinoma

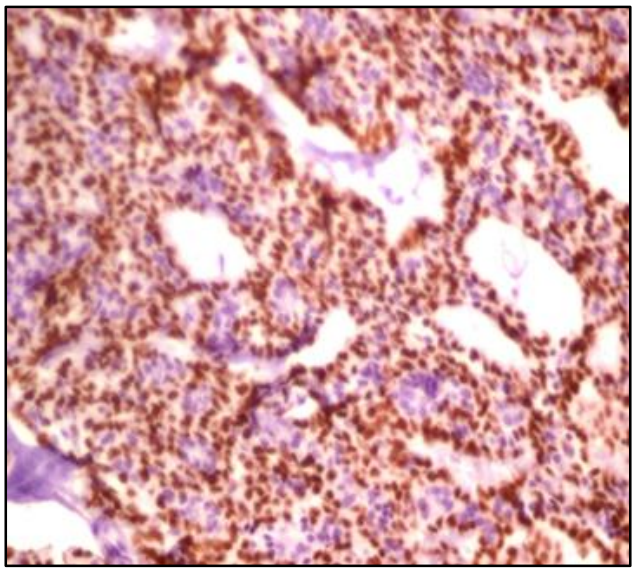

Figure 14. P63 Positive

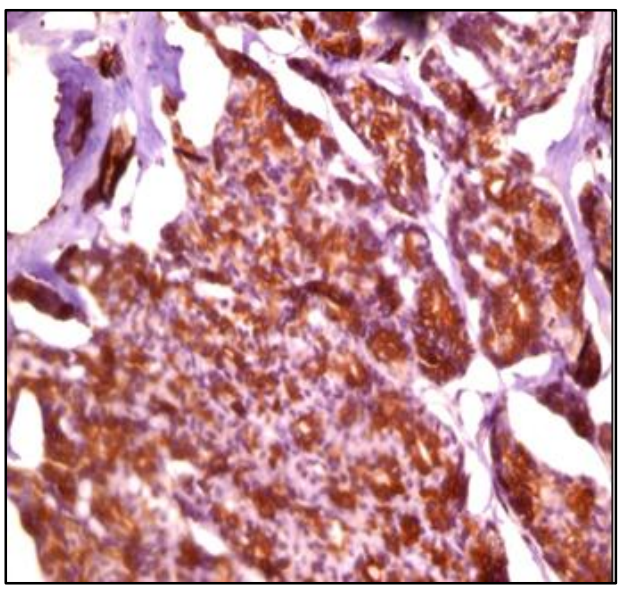

Figure 15. SMA Positive

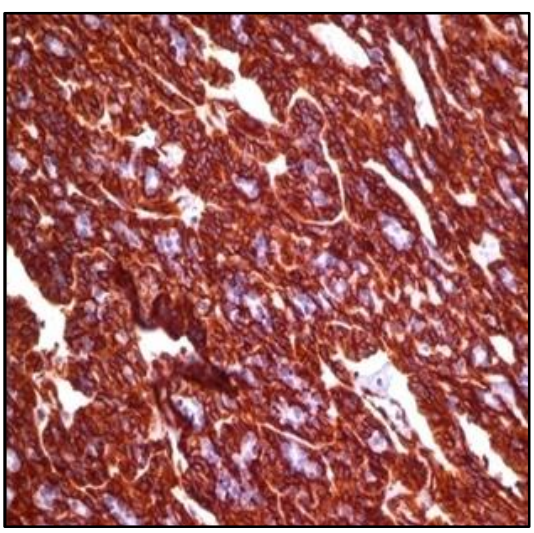

Figure 16. CD117 Positive

Figure 17, 18- IHC Images of Medullary Carcinoma Breast

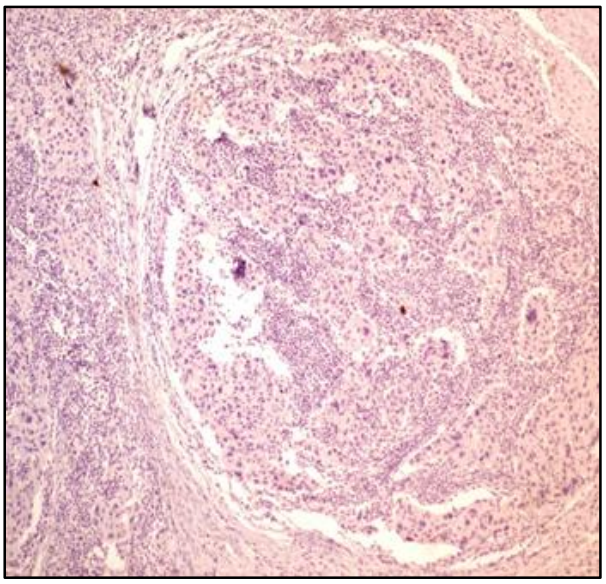

Figure 17. ER Negative

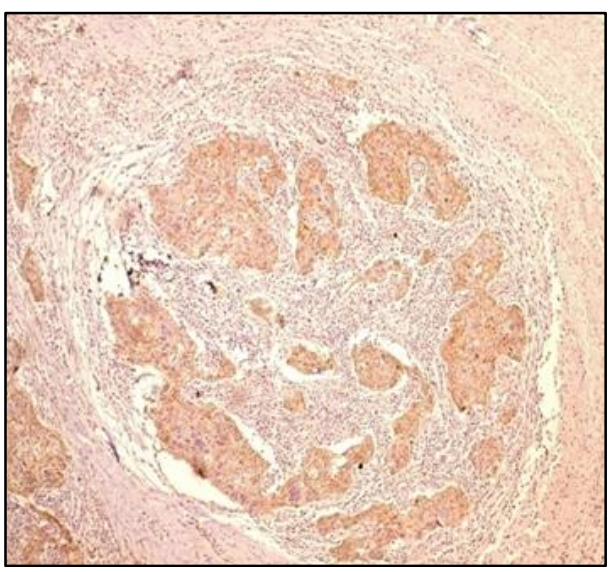

Figure 18. HER-2 Positive

DISCUSSION

Breast carcinoma is a major cause of mortality among women.[7] In recent years, advances in molecular biology of breast cancer have brought many changes in diagnosis and therapy of breast carcinoma patients.[6] The 13th International Breast Cancer Conference held in St. Gallen in March 2013 recognised progress in the pathological characterisation of tumour subtypes. Panel accepted that a surrogate definition of luminal disease could be made using a combination of ER, PR and Ki-67 without requiring molecular diagnostics.[7] However, Ki-67 marker could not be done in all the cases, so we could not classify luminal type into A and B subtypes.

Expression of hormone receptor is used for the choosing of endocrine therapy, whereas HER-2 overexpression identifies tumours sensitive to monoclonal antibody trastuzumab.[6] St. Gallen panel also proposed treatment recommendations for intrinsic subtypes of breast carcinoma. For management of special types of breast carcinomas, the panel classified them into two groups, i.e. endocrine responsive and the endocrine nonresponsive groups.[7] Endocrine responsive special type of breast carcinomas managed by endocrine therapy include cribriform carcinoma, tubular carcinoma and mucinous carcinoma. Endocrine nonresponsive special type of breast carcinomas managed by cytotoxic therapy include apocrine carcinoma, medullary carcinoma, adenoid cystic carcinoma and metaplastic carcinoma[7].These mostly belong to basal like subtype.

In the present study, most common subtype was IDC-NST similar to various studies in literature.[4,5] The special types of breast carcinomas (n-15) accounted for 16.66% of the cases. Most common subtype in the IDC-NST group was luminal subtype similar to Haque et al study.[8] In the special types subgroup, the breast carcinomas fell in various surrogate intrinsic subtypes.

The incidence of papillary carcinoma of breast was 5.2% during our study period. The mean age of presentation was 54 years similar to the literature.[9] Clinically, all the four females presented with palpable breast lump and axillary lymphadenopathy. Axillary lymph nodes showed benign reactive changes as seen in the literature.[9] Macroscopically, invasive papillary carcinomas are mostly grossly circumscribed. Resected specimen of one of the case showed a cyst measuring 3 x 3 cm with an intracystic papillary projection. Microscopically, papillary carcinomas of breast are often of Grade 2. In the present study, all the cases were of low grade. On immunohistochemistry, 100% of the tumours are ER positive and HER-2 negative and 80-100% are PR positive according to R. Yerushalmi et al study. Similar results were obtained in our study.[3] Papillary carcinomas are usually positive for ER receptor and favour a good prognosis with endocrine therapy.[7]

Metaplastic carcinoma refers to a heterogeneous group of the neoplasms characterised by admixture of adenocarcinoma with dominant areas of spindle cell, squamous and/or mesenchymal differentiation.[9] The WHO classifies metaplastic carcinoma into two types, epithelial and mixed type.[10] They constitute less than 1% of all the invasive breast carcinomas and commonly diagnosed in women more than 50 years of age. Metaplastic carcinoma is usually diagnosed with T2 disease with a mean size 3.4-4.4 cm.[9] In the present study, we received four cases of metaplastic carcinoma with similar clinicopathologic features. Metaplastic carcinomas show a basal like phenotype on immunohistochemistry according to literature.[9] All of our four metaplastic carcinoma cases also showed basal-like phenotype and therefore fall into endocrine nonresponsive category managed by cytotoxic therapy.[7] These tumours maybe associated with recurrences or metastasis.[9]

Carcinomas of breast characterised by the production of abundant extracellular or intracellular mucin are colloid carcinoma, mucinous cystadenocarcinoma, columnar cell mucinous carcinoma and signet ring cell carcinoma.

Pure mucinous carcinomas represent 1-4% of all the breast cancers.[9] The tumours usually present clinically as a

palpable lump. Microscopically, tumour is formed from abnormal cells that "float" in pools of the mucin. These are mostly well-differentiated carcinomas. On immunohistochemistry, they are positive for ER and PR and negative for HER-2 expression.[3] In the present study, the incidence was 2.5% and the mean age of presentation was 58.5 similar to the literature. All the cases showed a luminal type phenotype on immunohistochemistry and they are endocrine responsive with a favourable prognosis as per literature.

Medullary carcinoma is a well-circumscribed carcinoma, composed of poorly-differentiated cells arranged in large sheets with no glandular structures, scant stroma and a prominent lymphoplasmacytic infiltrate.[3] Medullary carcinoma represents 1-7% of all breast carcinomas and are associated with good prognosis.[3,11] The mean age of women with medullary carcinoma ranges from 45 to 52 years.[9] The mean age of medullary carcinoma patients in the present study was 48 years. On gene expression profiling, they show a basal-like phenotype in Bertucci et al study.[12] Of the two cases that were diagnosed as medullary carcinoma, one case showed a basal-like phenotype and the other case was of HER-2 subtype.

Adenoid cystic carcinomas are characterised histopathologically by a mixture of dual cell population of luminal and basaloid cells arranged in specific growth patterns.[13] The tumour represents 0.1% of the breast carcinoma.[9] Clinically, these tumours maybe painful and cystic. Pain is a prominent symptom due to the neural involvement.[3] The median age of adenoid cystic carcinoma cases in literature is 60 years.[13] In the present study, we diagnosed a single case of adenoid cystic carcinoma of breast whose age was 68 years. Generally, the tumour displays triple-negative phenotype.[13] Similar basal-like phenotype was obtained on immunohistochemistry in the current study.

There are very few studies published in literature, which have characterised these rare variants of breast carcinomas into molecular subtypes using immunohistochemistry. Subtyping of luminal type into Luminal A and Luminal B using Ki-67 marker would further help in treatment protocols. This however remains a limitation in our study and due to financial constraints surrogate molecular, subtyping could not be correlated with gene expression profiles of the breast carcinoma cases.

CONCLUSION

Breast cancer is a highly heterogeneous disease. Different types of this neoplasm exhibit variable histopathological and biological features, different clinical outcome and different response to systemic interventions. IDC-NST is the most common type and the special types constitute around 25% of breast carcinoma cases. Each special type of breast cancer has specific biologic and prognostic features, which present an opportunity for appropriate management and therapy of the patients.

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