CLINICAL, HISTOPATHOLOGICAL AND IMMUNOHISTOCHEMICAL CORRELATES OF BREAST CANCER: FINDINGS FROM A DESCRIPTIVE CROSS-SECTIONAL STUDY IN KERALA, INDIA

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Abstract

Introduction

Breast carcinoma is the most common malignancy among women, characterized by significant heterogeneity in histological and molecular profiles. Histological grading, immunohistochemical (IHC) characterization, and molecular subtyping are crucial for determining prognosis and therapeutic strategies. This study aims to describe the clinical, histopathological, and IHC characteristics of breast carcinoma in patients at a tertiary care center in Kerala, India.

Methods

This descriptive cross-sectional study was conducted at the Department of Pathology, Sree Gokulam Medical College, Kerala over a period of two years. Sixty female patients diagnosed with breast carcinoma by triple test (clinical examination, imaging, and biopsy) and undergoing surgical intervention were included. Data on clinical history, morphological characteristics, and IHC markers (ER, PR, HER2) were collected using a structured questionnaire. Histological grading was performed using the Nottingham modification of the Bloom-Richardson scoring system. Statistical analysis was done using SPSS version 16.

Results

The mean age of participants was 61 years, with 87% postmenopausal. The most common presenting symptom was a breast lump (100%). Tumors were predominantly located in the left

breast (62%) and the upper outer quadrant (60%). Infiltrating ductal carcinoma NOS was the most common histological subtype (51.7%). Most tumors were grade 1 (53%), followed by grade 2 (40%), and grade 3 (7%). IHC analysis revealed ER positivity in 68.3%, PR positivity in 48.3%, and HER2 positivity in 25% of cases.

Conclusion

Breast carcinoma predominantly affects postmenopausal women and is characterized by varying histological subtypes and IHC profiles. Early detection through improved awareness and self-examination, combined with accurate histological grading and molecular subtyping, can guide optimal treatment and improve outcomes.

Keywords: breast carcinoma, histopathologic grading, immunohistochemistry, Kerala

Introduction

Breasts are composed of specialized epithelium and stroma, which may give rise to both benign and malignant lesions. Carcinoma breast is one of the most common malignancies in women. There is one in eight chance of developing breast cancer in a woman living up to 90 years.[1]

Breast cancer is a disease of heterogeneity with a wide range of histology and its histological grade is the most important prognostic indicator. It can predict the overall survival rate of the individual with breast cancer. The histological grading is done by Nottingham histological grading, which is widely accepted. The treatment plan is made on the basis of histological typing, nuclear grading and molecular subtyping. It is desirable to grade breast cancers so that most appropriate therapeutic regimens can be chosen.

The objective of this study is to describe the clinical, histopathologic, immunohistochemical characteristics and prognostic grading of carcinoma breast reporting to a tertiary care centre in Thiruvananthapuram, Kerala, South India.

Methods

We designed a descriptive cross-sectional study to describe the clinical and histopathologic characteristics of carcinoma breast at the Department of Pathology, Sree Gokulam Medical College and Research Foundation, Thiruvananthapuram, Kerala, a tertiary care hospital in South India. We conducted the study between December 2022 and June 2024. The study population included all patients diagnosed with carcinoma breast using triple test (clinical examination, imaging and FNAC/core biopsy) and presenting to the Department of Pathology of the hospital.

We included all female patients meeting the diagnostic criteria who underwent surgical intervention at the hospital. We excluded male patients presenting with carcinoma breast from the study. For an expected proportion of 14.8% with an absolute precision of 10%, we estimated the sample size to be 49. We enrolled 60 participants meeting the inclusion criteria into the study.

We collected data using a structured questionnaire on clinical history including menstrual and obstetric history of study participants, morphological characteristics of surgical specimen, and ER, PR, HER2 status and molecular typing by immunohistochemistry. The grading of carcinoma was done using Nottingham modification of Bloom Richardson scoring system. Morphological examination of the carcinoma breast surgical samples was done. Immunohistochemical analysis of the 3 microtome sections of tissues was done for assessment of ER, PR and HER2 expression by Allred scoring system. We expressed various characteristics as proportions. We used SPSS Software version 16.0 for the data analysis.

We obtained approval of the institutional ethics committee (No. 31/381/11/2022) prior to initiation of the study and obtained written informed consent from all study participants. No additional financial burden was imposed on the study participants. The study posed minimal risk to participants. Data collected was anonymised and coded before analysis.

Results

We included 60 participants who met the inclusion criteria and underwent mastectomy at Sree Gokulam Medical College and Research Foundation, Thiruvananthapuram, India during the period 2022-2024 for the study. The mean (SD) of age (years) of the study participants was 61

(11) years. Of the 60 study participants, 22 (36%) belonged to the 61-70 years age group,

followed by 16 (26%) in the 51-60 years age group, 10 (17%) in the 41-50 years age group and 9

(15%) in the 71-80 years age group respectively. All participants presented with complaints of

lump in the breast (n = 60; 100%) with 51 (85%) presenting with pain in the breast. None of the

participants had family history of carcinoma breast. Among the study participants, 8 (13%) were

premenopausal and 52 (87%) were postmenopausal; and 10 (16.7%) had past history of atypical

ductal hyperplasia of breast. (Table 1)

Table 1. Characteristics of study participants

Characteristic		N = 60	
Age (years), *mean (sd)*		61	(11)
Age group (years), *n (%)*			
	21-30	1	(2)
	31-40	1	(2)
	41-50	10	(17)
	51-60	16	(26)
	61-70	22	(36)
	71-80	9	(15)
	81-90	1	(2)
Menstrual history			
	Pre-menopausal	8	(13)
	Post-menopausal	52	(87)
Past history of atypical ductal hyperplasia		10	(16.7)

Most (n = 37, 62%) presented with swelling in the left breast. Of 60 study participants, 36 (60%)

presented with involvement of upper outer quadrant, followed by 21 (35%) in the lower inner

quadrant and 3 (5%) in the upper inner quadrant of the breast. The median (range) tumour size

was 4.8 (0.25-12.25) cm with 27 (44%) measuring above 5 cm; 19 (32%) measuring less than 2

cm and 13 (22%) measuring between 2-5 cm. Among the study participants, 50 (83%) had

irregular shaped tumours and the remainder (n = 10, 17%) had trucut specimens. Seven (11.7%)

participants had fungated skin over the swelling; 22 (37%) had dimple over the swelling;

39(65%) had retraction of lymph nodes and 24 (40%) had ulceration of overlying skin. 56 (93%)

of 60 participants had regional lymph node enlargement. (Table 2)

Table 2. Gross characteristics of tumours of study participants

Characteristic		n	(%)
Site of breast lesion, *n(%)*			
	Left	37	(62)
	Right	23	(38)
Quadrant involvement			
	Upper outer	36	(60)
	Upper inner	3	(5)
	Lower outer	0	(0)
	Lower inner	21	(35)
Size of tumour, *cm*			
	0	1	(2)
	< 2	19	(32)
	2 – 5	13	(22)
	> 5	27	(44)
Shape of tumour			
	Irregular	50	(83)
	Trucut	10	(17)
Overlying skin			
	Normal	53	(88.3)
	Fungated	7	(11.7)
Dimpling of skin		22	(37)
Retraction of nipple		39	(65)
Ulceration of overlying skin		24	(40)
Regional lymph node enlargement		56	(93)

Infiltrating ductal carcinoma NOS (Figure1) was the most common histological type of breast

carcinoma among study participants (n = 31, 51.7%) followed by 13 (21.7%) participants with

invasive lobular carcinoma. Table 3 shows the different histological types of breast carcinoma

among study participants. We did Scarff-Bloom-Richardson grading of the tumours based on

tubule formation, nuclear pleomorphism and mitotic count. Majority (n = 32, 53%) were of grade

1, 24 (42%) were grade 2 and 4 (7%) were grade 3. Immunohistochemistry showed that 41

(68.3%) were ER positive (Figure 2), 29 (48.3%) were PR positive (Figure 3) and 15 (25%) were

positive for HER2 (Figure 4). All 29 cases positive for PR were positive for ER as well.

Table 3. Histologic characteristics of breast carcinoma among study participants

| Characteristic	n	(%)
Histologic subtype		
Infiltrating ductal carcinoma (NOS)	31	(51.7)
Invasive micropapillary carcinoma	4	(6.7)
Mucinous carcinoma	3	(5)
Invasive lobular carcinoma	13	(21.7)
Metaplastic carcinoma	2	(3.3)
High grade ductal carcinoma in situ, Paget's disease	1	(1.7)
Invasive micropapillary carcinoma with apocrine differentiation	2	(3.3)
Pleomorphic lobular carcinoma	2	(3.3)
Invasive ductal carcinoma with medullary features	1	(1.7)
Metastatic breast carcinoma	1	(1.7)
Scarff-Bloom-Richardson Grading		
Grade 1	32	(53)
Grade 2	24	(40)
Grade 3	4	(7)
Immunohistochemical analysis		
ER positive	41	(68.3)
PR positive	29	(48.3)
HER2 positive	15	(25)
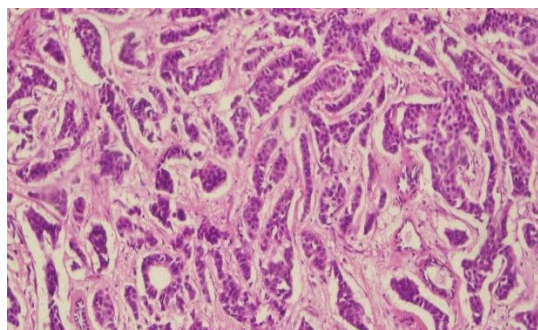
Figure 1: Photomicrograph showing Invasive Ductal Carcinoma NOS (H&E x10)
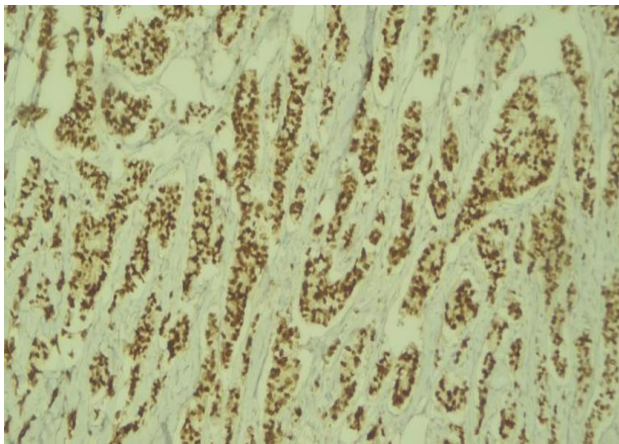

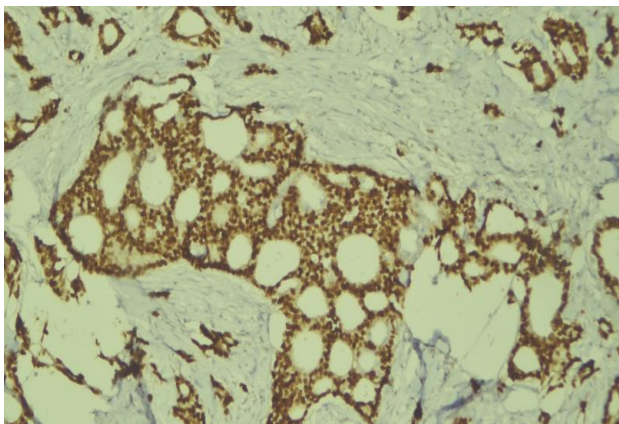Figure 2: Immunohistochemistry showing ER nuclear positivity

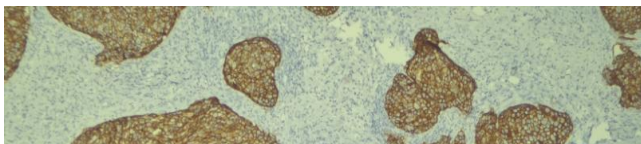Figure 3: Immunohistochemistry showing PR nuclear positivity

Figure 4: Immunohistochemistry showing HER2 NEU membrane positivity

Discussion

This descriptive cross-sectional study enrolled 60 participants who underwent mastectomy at a tertiary care hospital in south India during the time period December 2022 to June 2024. The mean age of study participants with breast carcinoma observed in the present study was 61 years. Highest proportion of study participants were in the age groups 51-60 years and 61-70 years. Previous studies corroborate that over 80% of cases of breast carcinoma are reported in females aged 50 years and above.[1] All participants in the study presented with a lump in the breast as the dominant symptom; and more than three-fourth of participants presenting with pain in the breast also. Similar findings were observed in previous studies.[2,3,4] Costa WA et al described pain as the presenting complaint in 20-50% of patients with breast carcinoma in the initial stages and in upto 90% of patients with terminal and metastatic carcinoma.[5]

More than one-half of study participants had carcinoma of the left breast. The side involvement is not a clearly described finding, and the mechanism of side involvement has not been clearly elucidated. Nearly one-fifth of study participants had past history of atypical ductal hyperplasia. Atypical ductal hyperplasia is associated with 2.6 times higher odds of development of breast carcinoma in the future decade.[6,7] Though family history of breast carcinoma is a well described risk factor, none of the participants included in the present study had positive family history. Persons with family history of breast carcinoma have 3.5 fold higher risk of breast carcinoma. [2,3,4,6,7] Over three-fourth of study participants had attained menopause. The risk of breast carcinoma increases as menopause is attained. [6,7]

Nearly one-half of study participants presented with tumour size more than 5 cm. Late presentation is a factor associated with poor prognosis. [8,9] Two reasons could contribute to this finding in the present study – higher proportion of post-menopausal women enrolled in the study, and lack of adequate self-examination to detect early lesions. Increasing age increases the risk of breast carcinoma and metastatic breast disease.

Malignant lesions of breast are typically described with irregular margins.[8,9] Over one-tenth of participants had fungated skin over the lesion indicating the presence of locally invasive breast lesions which would erode or disrupt the normal architecture of overlying skin leading to the fungated appearance. [8,9,10] Dimpling is usually observed in inflammatory breast carcinoma and is thought to be due to blockage of lymphatic channels in the skin over the breast and is commonly seen in inflammatory breast carcinoma. [8,9,10] Dimpling could also be due to invasion of Cooper's ligament by the carcinoma and subsequent adherence to skin. [6,7, 8,9,10] 37% of participants in the

present study reported with dimpling of skin over the lesion. Two-thirds of study participants had retraction of nipple. A possible mechanism for this finding is the invasion and shrinkage of large ducts in the breast leading to retraction of nipple. [8,9,10] Ulceration of overlying skin was reported by 40% of study participants. Local invasion of malignant cells into the skin and subcutaneous tissue produce ulcerations. [8,9,10] Majority (93%) of study participants also presented with regional lymph node enlargement. Regional lymph node enlargement is a common finding in breast carcinoma and is due to local lymphatic spread of malignant cells and the inflammatory process associated with malignancy. [8,9,10] Upper outer quadrant was the commonest site (60%) of tumour in study participants. This could be due to the larger amount of breast tissue present in this quadrant. [8,9,10,11,12] The association of higher incidence in upper outer quadrant with the use of under arm cosmetics containing paraben and other carcinogens is yet to be proven. [13,14]

Infiltrating ductal carcinoma not otherwise specified (NOS) was the commonest histologic subtype of malignancy encountered among study participants with over one-half of study participants belonging to this group. Similar findings were observed in comparable studies with 55% of all breast carcinomas being infiltrating ductal carcinoma. [14,15] Invasive lobular carcinoma was diagnosed in over one-fifth of study participants. Sinn HP et al. has described invasive lobular carcinoma in 5-15% of patients with invasive breast carcinoma. There are reports of increasing incidence of invasive lobular carcinoma in post-menopausal women, with possible relationship with hormone replacement therapy. Invasive micropapillary carcinoma with apocrine differentiation, pleomorphic lobular carcinoma and metaplastic carcinoma were seen in 3.3% of study participants each.

Over one-half of study participants had grade-1 lesion as per Scarff-Bloom-Richardson grading system indicating good prognosis. 40% of study participants had grade-2 lesions indicating poor prognosis and 7% with grade-3 lesions indicating very poor prognosis. On immunohistochemistry, over two-thirds of participants showed ER (estrogen receptor) positivity, nearly one-half showed progesterone receptor (PR) positivity and one-fourth showing HER2 positivity. Previous studies describe positivity for ER, PR or both in breast carcinoma to be 70%. (ref) Binding of estrogen to estrogen receptors (ER) present on breast tissue results in a cascade of events leading to alterations in regulation of cell cycle, DNA replication, cellular differentiation, apoptosis and angiogenesis. Cross-talk between these receptors have also been established indicating a higher activation of both PR and HER-2 downstream signalling in ER positive patients and vice versa. ER and PR positivity decreases with increasing grades of tumor while amplification of HER 2 increases with increasing grades of tumor. ER, PR negativity and HER2 amplification is associated with larger tumor size and higher grade.

The strength of this study is that it comprehensively describes the gross appearance, histologic type and immunohistochemical characteristics of breast carcinoma in a tertiary care hospital in South India. This study has a few limitations. Being a descriptive cross sectional study in a tertiary care setting, it may not reflect the actual prevalence of different histologic types in the community. The study also does not analyse the association of various factors with outcomes.

Conclusion

Breast carcinoma is commonly reported in females aged 50 years and above with breast lump and pain in breast as the common presenting symptoms. Infiltrating ductal carcinoma not

otherwise specified (NOS) was the commonest histologic subtype and over two-thirds of patients had ER positivity. Over one half of patients had grade-1 tumour based on Scarff-Bloom-Richardson grading. Histopathological typing, Grading and IHC based molecular subtyping status help to ascertain correct treatment and further prognosis of patients.

REFERENCES

1. Collins LC, Schnitt SJ. Breast. 4th ed. Lippincott Williams & Wilkins; 2012.

2. Macias H, Hinck L. Mammary Gland Development. Wiley Interdiscip Rev Dev Biol. 2012;1(4):533‑57.

3. Pandya S, Moore RG. Breast development and anatomy. Clin Obstet Gynecol. 2011 Mar;54(1):91‑5.

4. Visvader JE, Stingl J. Mammary stem cells and the differentiation hierarchy: current status and perspectives. Genes Dev. 2014 Jun 1;28(11):1143‑58.

5. Costa WA, Monteiro MN, Queiroz JF, Gonçalves AK. Pain and quality of life in breast cancer patients. Clinics. 2017 Dec;72(12):758‑63.

6. Kurian AW, Fish K, Shema SJ, Clarke CA. Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. Breast Cancer Res BCR. 2010;12(6):R99.

7. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst. 1975 Aug;55(2):231

8. Weigelt B, Geyer FC, Reis-Filho JS. Histological types of breast cancer: how special are they? Mol Oncol. 2010 Jun;4(3):192‑208.

9. Kerner H, Lichtig C. Lobular cancerization: incidence and differential diagnosis with lobular carcinoma in situ of breast. Histopathology. 1986 Jun;10(6):621‑9.

10. Rosen PP. Rosen's Breast Pathology. Lippincott Williams & Wilkins; 2001-1028 p.

11. Menes TS, Kerlikowske K, Lange J, Jaffer S, Rosenberg R, Miglioretti DL. Subsequent Breast Cancer Risk Following Diagnosis of Atypical Ductal Hyperplasia on Needle Biopsy. JAMA Oncol. 2017 Jan 1;3(1):36‑4112.

12. Surakasula A, Nagarjunapu GC, Raghavaiah KV. A comparative study of pre and post-menopausal breast cancer: Risk factors, presentation, characteristics and management. J Res Pharm Pract. 2014;3(1):12‑8.

13. Wang YA, Jian J-W, Hung C-F, Peng H-P, Yang C-F, Cheng H-CS, et al. Germline breast cancer susceptibility gene mutations and breast cancer outcomes. BMC Cancer [Internet]. 2018 Mar 22 [cited 2020 Dec 10];18.

14. Peeters PH, Verbeek AL, Krol A, Matthyssen MM, de Waard F. Age at menarche and breast cancer risk in nulliparous women. Breast Cancer Res Treat. 1995;33(1):55‑61.

15. Chlebowski RT, Chen Z, Anderson GL, Rohan T, Aragaki A, Lane D, et al. Ethnicity and breast cancer: factors influencing differences in incidence and outcome. J Natl Cancer Inst. 2005 Mar 16;97(6):439‑48.