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Original Article

Correlation of Molecular Subtypes with Clinico-pathological Parameters in Breast Carcinoma

Aisha Akbar, Ghazala Mudassir, Mariam Abid,Hania Naveed, Mahwish Majeed
Department of Pathology, Shifa College of Medicine, Islamabad

Abstract

Background: To determine the correlation between clinic-pathological parameters, like age of the patient, size of the tumour, histologic type and grade with molecular subtype.

Methods : This observational study included cases of breast cancer (n=50) . Histological grade was assessed according to Nottingham modification of Bloom-Richardson system. Representative sections with tumour and the adjacent normal tissue (internal control) were processed for ER, PR and HER-2neu immune-histochemical staining. The scoring of ER and PR was carried out using Allred scoring system. Molecular subtypes were defined as, triple negative/basal type(HER 2 -,ER- and PR-), hormone receptor(HR) +,HER2-/luminal A(HER2-, ER+ and PR+ or -), HR+,HER2+/luminal B(HER2 +,ER+ and PR+ or-), HR-,HER2+/HER2 enriched(HER2+, ER- and PR -).

Results: Majority (96%) were infiltrating ductal carcinoma, one was invasive lobular carcinoma and one was colloid carcinoma. Three cases (6%) grade 1 carcinoma were recorded of which one case (2%) each was of luminal A, luminal B and HER2 enriched type. There were 23 (46%) grade 2 cases of which 8(16%) were luminal A, 7(14%) of luminal B, 7(14%) of HER2 enriched and one (2%) was basal like. There were 24(48%) grade 3 cases of which 6(12%) were luminal A, 9(18%) of luminal B, 6(12%) were HER2 enriched and 4(8%) were basal like.

Conclusion: Along with other variables, molecular subtype is important in predicating prognosis of carcinoma breast .Luminal A cancers are more common in older age, while Luminal B are common in younger age group.

Key Words: Carcinoma breast,Molecular Subtypes, Estrogen receptor, progesterone receptor, Human epidermal growth factor receptor

Introduction

Breast carcinoma is a common malignancy among women worldwide and is the second leading cause of death by a cancer.[1] It constitutes 22 % of all the cancers occurring in females which is more than twice the prevalence of cancer at any other site.[2] In Karachi it accounts for one third of cancers in females with an annual age standardized incidence rate of world of 53.8 per 100,000 population.[3] Prognosis of breast carcinoma depends on the tumour size, histological type and lymph node metastasis at the initial presentation. Management of the malignancy is greatly influenced by the estrogen progesterone receptors (ER, PR) and HER-2 neu receptor positivity. As the degree of tumour differentiation is positively correlated with ER and PR, it is now a standard practice to determine the hormonal status of the biopsy specimen prior to the start of therapeutic intervention.[4] Changes in the breast tissue are most profound during the reproductive years. In the second part of the ovulatory cycle under the influence of estrogens and progesterone there is both cell proliferation and increase in the number of acini per lobule.[5] Estrogen receptor is found in 50-80% of breast cancers where estrogen acts as an important inducer of cell proliferation. Hormonal treatments given to antagonize estrogen were met with considerable success e.g. Tamoxifen blocks the ER and arrests the cell cycle.[6]

PR is expressed in 60-70% of invasive breast carcinomas with a higher positivity in older age and post-menopausal women. Her -2 neu also known as C-erb B2 is a proto-oncogene located on chromosome 17 It is amplified and the protein HER2 is overexpressed in 15-25% of invasive breast carcinoma Her2 is a negative predictor of survival relapse in patients with lymph-node-positive-breast-cancer.[7]

Breast cancer is described on basis on Nottingham grading system and further stratified into molecular subtypes.[8]This subtyping is done on the basis of immune-histochemical examinations for hormonal receptors and Human epidermal growth factor receptor (HER2).[9] Molecular subtypes are found to have different risk factors, recurrence patterns, recurrence rates and survival curves. In addition therapy is not the same, and depends on the molecular subtype.

Patients and Methods

This observational study was carried out at the section of histopathology, Pakistan Institute of Medical Sciences, from January 2015 to October 2016. Fifty cases of breast carcinoma who underwent biopsy or mastectomy for breast carcinoma, were included. Specimens were routinely processed and fixed overnight in 10% buffered formalin. They were examined grossly according to standard guidelines. Four to five micrometer thick formalin fixed, paraffin embedded tumour sections were stained with Haematoxylin and Eosin. Histological grade was assessed according to Nottingham modification of Bloom-Richardson system. Representative sections with tumour and the adjacent normal tissue (internal control) were processed for ER, PR and HER-2neu immune-histochemical staining. The scoring of ER and PR was carried out using Allred scoring system and score of 3 or more was considered positive. Score 3+ for HER-2 was taken as positive. The results were correlated with tumour size, type, grade and age of the patient with molecular subtypes. Molecular subtypes were defined as; Triple negative/Basal type(HER 2 -,ER- and PR-), Hormone receptor(HR) +,HER2-/luminal A(HER2-, ER+ and PR+ or -), HR+,HER2+/luminal B(HER2 +,ER+ and PR+ or-), HR-,HER2+/HER2 enriched(HER2+, ER- and PR -).

Results

Mean age of the patients was 52.46 ± 10.4years, ranging from 25 to 81 years. Thirty eight (76%) cases were 46 years and above. Only 12 (24%) cases were less than 46 years of age. Luminal A, HER2 and basal like were found in age range of 46-55 years but luminal B type was found in a wider age range of 35-65 years. Two ER positive cases were of grade 1 and one each case belonged to luminal A and B. There were 15 ER positive cases of grade 2, 8 belonging to luminal A and 7 cases were of luminal B type (Figure 1&2). Fifteen of the ER positive cases were of grade 3 with 6 belonging to luminal A and 9 belonging to luminal B. Thirty one cases were HER2 positive with 17 belonging to luminal B and 14 belonging to HER2 enriched type (non luminal). Fourteen of the HER2 were of grade 2 and 15 were of grade 3.Predominant morphology was infiltrating ductal carcinoma (48 cases, 96%) of which 14(28%) were luminal A, 16(32%) were luminal B, 14(28%) HER 2 enriched and 4(8%) were basal type. (Table 1) One case (2%) was of invasive lobular with molecular subtype of luminal A and one case (2%) was of colloid carcinoma with a molecular subtype of luminal B: both were grade 3 carcinomas. Luminal cancers were 64% of the total cases of breast carcinoma with luminal A comprising 30 % and luminal B were 34%. The mean age for luminal A subtype was 55 years and for luminal B was 53 years. HER2 enriched cases were 28% with a mean age of 48.5 years whereas basal type were 8% with a mean age 50 years. Luminal A, HER2 enriched and basal type were found in age range of 45-55years, whereas luminal B had involved a wider age range of 35-65 years of age.In majority (84%), the tumour size was less than 5cm with only 8 cases (16%) presenting with tumor size more than 5 cm. Three cases out of 4 basal type were less than 5 cm at presentation.

Table 1: Correlation between molecular subtypes , grading and histopathology

Molecular subtype	Grade1	Grade2	Grade3	Histological type-IDC	Histological type-Others	Age range	Size <5 cm	Size >5 cm
Luminal A (n=15)	1	8	6	14	Invasive lobular- 1 case- grade 3	46-55	11	4
Luminal B (n=17)	1	7	9	16	Colloid carcinoma-1 case -grade3	36-65	14	3
HER2 enriched (n=14)	1	7	6	14	-	46-55	14	-
Basal like (n=04)	0	1	3	4	-	46-55	3	1
Total (n=50)	3	23	24	48	2		42	8

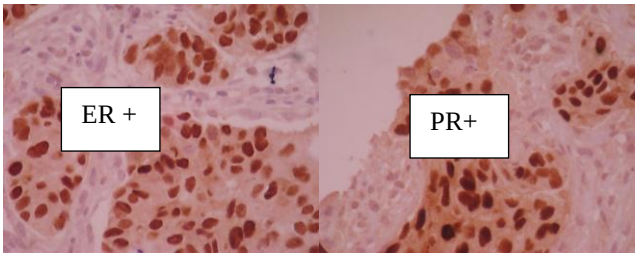

Figure 1:Strong nuclear immunostaining for hormonal receptors

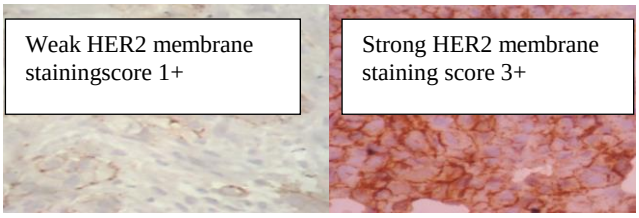

Figure 2:Patterns of HER2 immunostaining

Discussion

Breast carcinoma is the most common malignant tumour in females.[10,11]Breast tissue is normally responsive to ovarian hormones and an imbalance promotes the development of a neoplastic process.[12]A tumour with a positive hormone receptor responds to anti hormonal therapy.[13] Prognosis of breast carcinoma

is dependent on many prognostic factors like age, histologic type, grade, tumour size and lymph node involvement but receptor status has proved to be the most important prognostic marker which has an effect on 5 year survival and also on mortality rate and disease free survival rate.[13,14]

The mean age in the present study was 52 years while it was a bit lower in a study done in Nepal by Pathak2011. [15]Age mean value was similar to studies done by Malik in 1994[16] and Aryandono in 2006.[17]Tumor size in present study at the time of presentation wasT2(2-5 cm) in 84% and T3(>5 cm) in 16% which is slightly higher to study done by Hashmi et al[18] where the T2 was 72% and T3 was 14.3%.In our study ER positivity increased with increasing age of the patient. ER positivity associated with HER2 positivity in luminal B subtype is an aggressive type of breast cancer and more prevalent in younger patients. This observation was also noticed by Hashimet al.[18]

Predominant histological type was infiltrating ductal carcinoma (96%) in the present study which is similar to studies done worldover.[19-22] The most prevalent molecular subtype in present study were luminal type(64%) and similar trends were seen in studies done in Karachi, Italy and USA except a study in Saudi Arabia where Her2 enriched type was almost equivalent to luminal cancers[19-22]. Luminal B were more prevalent in study done by Hashmi and in Saudi Arabia with almost equal distribution in both luminal A and B types(30 and 34 %) in the present study[19,21]. This pattern of distribution highlights the heterogeneity of breast carcinoma molecular subtype's world over.

Table 2: Molecular subtypes of carcinoma breast- correlation with other studies

	Present study	Hashmi et al	Caldarella et al	Bhargava et al	Al Tamimi et al
Luminal cancers (%)	64	62.7	70	72	19.9
Luminal A (%)	30	31	34	55	3.9
Luminal B (%)	34	69	36	17	16
HER2 type(%)	28	-	10.2	4	17.3
Basal type(%)	8	-	19	15	10

In the present study HER 2 positive cases were 31 cases (62%), with luminal B being 34% and HER 2 enriched(non luminal) were 28%. Study done by Hashmi et al showed 41% HER2 positive cases with luminal B being 52.2 % and HER 2 enriched being 47.8% (Table 2). Present study revealed only one case of each category in grade one while almost equal number of cases of both molecular subtypes was seen in grades 2 and 3.[19] Hashmi et al found higher grade in non luminal type, thus finding a predictive value for ER positivity with HER2 positivity as grades of luminal B were lower in his study.[18] This was not found in present study.

Conclusion

1. Prognosis of breast carcinoma depends on a number of variables like type, grade, age, size of tumor at presentation and molecular subtype. For every patient these parameters should be determined to devise a personalized therapeutic regimen.
2. Luminal cancers are most prevalent. Luminal A incidence increased with increasing age whereas luminal B were found in a younger age group.

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