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CLINICOPATHOLOGIC FEATURES AND MOLECULAR SUBTYPES OF BREAST CANCER IN FEZ-MEKNES REGION (MOROCCO): A STUDY OF 390 PATIENTS

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ABSTRACT

Background. Breast cancer is the most common malignant tumor in women; it is different from other malignant tumors in that it appears to be heterogeneous in outcomes. Although individual molecular markers were introduced in the field of breast cancer management many years ago, the concept of molecular classification was raised after the introduction of global gene expression profiling and the identification of multi-gene classifiers.
Methods. This is a prospective study in the department of Pathology at the Hassan II University Hospital of Fez. A descriptive analysis of clinical, histological and immuno-histochemical characteristics of four molecular subtypes of breast cancer was performed (Luminal A, Luminal B, HER2 over expression and triple negative phenotypes).
Results. In our survey, 390 cases of breast mammary carcinoma were observed; the most common subtype was luminal B. The luminal A subtype is significantly associated with the presence of ductal carcinoma in situ. 64% of triple negative phenotype tumors were Grade III SBR, and 57% of HER 2 phenotype tumors were Grade II SBR with a significant difference. 90% of the infiltrating lobular carcinomas are of luminal phenotype.
Conclusions. Our study shows that the luminal subtype B is the most common molecular subtype, which is a peculiarity of our series. There was also a significant difference between the molecular sub-types and the SBR grade, which is in line with previous observations.

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INTRODUCTION

Breast cancer is the most common cancer in Morocco [1] and worldwide. Hence the explosion of genomics technology in this domain has resulted in a wave of efforts to use these advances to improve patient care.
Gene expression microarray studies have identified distinct molecular tumor classes based on simultaneous expression analyses of thousands of genes in a single experiment. Sorlie and Perou have first defined five subtypes of prognosis and different therapeutic response: luminal A, luminal B, normal, Her-2, and basal [2]. Although identification of intrinsic subtypes is most precise using molecular technologies, where such assays are unavailable, surrogate definitions of subtype can be obtained by IHC measurements of ER, PgR, Ki-67 and HER2 with in situ hybridization confirmation, where appropriate [3-4]. The aim of our prospective study 2008-2011 (390 cases), is to correlate these different molecular subtypes with clinical and histopathological data.

MATERIALS AND METHODS

This is a prospective study in the department of Pathology at the Hassan II[d] University Hospital of Fez. To complete this work, we have collected cases of breast cancers diagnosed in the service of pathology between January 2008 and September 2011.

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According to the results for the four IHC markers (ER, PR, HER-2, Ki-67), four molecular subtypes were identified, Using the classification outlined in the 13th St. Gallen International Breast Cancer Conference: Luminal A phenotype was defined as expressing ER+ and (or) PR+, HER-2- and Ki-67 <14%. Luminal B phenotype was defined as expressing hormonal receptors with overexpression of HER2, or with a Ki67>14%. HER-2 over expression phenotype: ER-, PR-, HER+, any level of Ki-67; and triple negative phenotype: ER-, PR-, HER-, and Ki-67 any level [5].

A descriptive analysis of clinical, histological and immunohistochemical characteristics of the patients was performed.

When comparing groups, we used the classical parametric tests (Khi2 test, Student's test, ANOVA) according to the nature of the variables to be compared. For each statistical test used, the test was considered significant when p (degree of significance) was less than 0.05. Statistical analysis is performed using the Epi-info software (version 3.3.2).

RESULTS:

In our study, 390 cases of breast mammary carcinoma were observed, the most common subtype in our series was luminal B, found in 40.5% of the patients(**figure 1**).

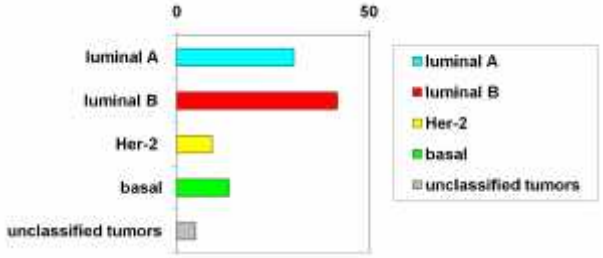

Figure 1: Distribution of breast tumors according to molecular classification of breast cancer

The average age was 48 years with a median of 46 years [22- 99]. **Table I** lists a variety of clinical and pathologic factors for each group of breast molecular subtypes. When grouped according to histological type, the molecular subtypes showed a significant association between luminal A and B subtypes and invasive lobular carcinoma (p <0.00001). Histological grade was significantly different : Grade 1 tumors were detectedin 28.3% of luminal A subtype tumors, 9.6% ofluminal B subtype tumors, 9.8% of HER2 subtype tumors, and 4.0% of triple negative subtypetumors. Grade 3 tumors were detected in 12.5% of luminal A subtype tumors, 30.6% of luminal B subtypes, 34.1% of HER 2 subtypes, and 64% of the triple negative subtype tumors. Lympho-vascular invasion was seen in 71.2% of the 163 luminal B subtype. Carcinoma in situ was detected in 55.0% of luminal A tumors, 39.5% of luminal B tumors, 41.5% of HER2 subtype tumors and 25.5% of triple negative tumors. No pathologic correlation was observed between the molecular subtypes according to the presence of tumor necrosis. Tumor size was significantly different between molecular subgroups: T1was found in 42.9% of luminal A subtype, 31.8% of luminal B subtype, 9.1% of HER2 subtype and 12.5% of triple negative subtype.

Pathologically proven axillary lymph node disease occurred statistically significantly more frequently in HER2 subtype tumors (86.7%) than in triple negative subtype tumors (81.3%), luminal B tumors (68.8%) and luminal A tumors (52.4%).The presence of metastasis was significantly correlated with the triple negative subtype Found in 26.7% of patients, whereas it is retrieved at only 4.5% of luminal A subtype tumors, 12.5% of luminal B subtype tumors and 17.9% of HER2 subtype tumors.

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Table I: Distribution of molecular subtypes depending on morphologic and clinical data

Subtype (effective)	luminal A (n 119)	luminal B (n 163)	Her 2 (n 36)	Basal (n 53)	Un classifiable (n 19)	p value
Histological type %						p<0,0001
IDC-NOS	30.5	41.1	10.9	13.9	3.6	
ILC	47.6	42.9	4.8	0.0	4.8	
Others	25.0	8.3	16.7	50.0	0.0	
SBR grade %						p=0.0001
I	28,4	9,6	9,8	4	15,8	
II	59,2	59,9	56,1	42	26,4	
III	12,5	30,6	34,1	64	57,9	
LVI %						p=0,29
Presence	60.8	71.2	75.6	64.4	63.2	
Absence	39.2	28.8	24.4	35.3	36.8	
DCIS %						p=0,0014
Presence	55,0	59,5	41,3	23,5	78,9	
Absence	45,0	60,5	58,5	74,5	21,1	
tumor size cm						p=0,0003
T1	42.9	31.8	9.1	12.5	25.0	
T2	34.5	44.76	45.5	46.9	25.0	
T3	14.3	18.8	27.3	15.6	12.5	
T4	8.4	4.7	18.2	25.0	37.5	
	52,1	68,8	86,7	81,3	53	p= 0,0066
lymph node involvement %						
Metastasis %	4,5	12,5	17,9	26,7	28,6	P= 0,0030

IDC-NOS: invasive ductal carcinoma not otherwise specified; ILC: invasive lobular carcinoma; LVI: lympho-vascular invasion; DCIS: ductal carcinoma in situ4

DISCUSSION

Breast cancer is different from other malignant tumors in that it appears to be heterogeneous in outcomes. The effect of treatment to the patient and the prognosis are not the same, even though the histological types and the treatment methods used are the same. Therefore, the molecular classification of breast cancer can provide an important basis for individualized treatment and prognosis.

Our study shows that luminal B subtype is the most common molecular subtype representing 41.8% of cases, in contrast to literature data where the luminal A subtype is the most frequent (**Table II**) [6-13].

Table II: Overall distribution of different molecular subtypes based on ethnicity

	Luminal A	Luminal B	HER2	Basal
. Our series (Fez-Meknes region - Morocco)	30.5 %	41.8 %	9.2%	13.6 %
. Ahmadaye et al (Casablanca-Settat Region-Morocco)	41.4 %	10.4 %	5.3 %	11.4 %
. Carey et al. (US)				
African-American women	47.4 %	12.4 %	8.1 %	26.5 %
Non African American women	54.0 %	17.3 %	5.6 %	16.0 %
Chukwuemeka et al (African-American woman)	55.1 %	11.8 %	11.5 %	21.2 %
. Junichi et al. (Japan)	63.0 %	20.0 %	7.0 %	8.0 %
. Munirah et al. (Malaysia)	57.6 %	6.9 %	14.3 %	7.4 %
. Su et al. (US)	48.5 %	16.7 %	13.6 %	12.9 %
Jonsson et al (Sweden)	26.0 %	19.0 %	9.0 %	22.0 %
. Spitale et al. (Switzerland)	73.2 %	13.8 %	5.6 %	7.4 %

Luminal B breast cancers are a clinically important subgroup associated with intermediate prognosis between luminal A subtype and other molecular subtypes of breast cancer. This subtype is characterized by having increased expression of HER2-associated genes (ie, ERBB2 and GRB7) and a cell proliferation signature that includes the expression of MKI67, CCNB1, and MYBL2, which have been associated with tamoxifen resistance [14].

We found a significant association between the luminal A subtype and association with carcinoma in situ, which underscores the hypothesis of a continuum between carcinoma in situ and invasive

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carcinoma of low grade [15]. This is supported by various studies showing that in on hand, luminalA tumors show high expression of ER and PR-related genes, GATA binding protein 3, low expression of proliferation-associated genes, and lack expression of Her-2. In the other hand, approximately 50~75% of ductal carcinoma in situ were ER and/or PR-positive tumors, and reported expression rates of ER and/or PR in microinvasive carcinoma ranged from 50~68% [16]. Expression of HR often correlated with low proliferation and better survival.

This study has also shown that HER2 phenotype tumors are associated with the highest rate of lymph node involvement (86.7% of cases), which is a group of tumors associated with poor prognosis.These findings are in line with previous observations [17].

There was a significant association between triple negative phenotype and the presence of distant metastases, which are found in 26% against 4.5% for luminal A subtype (p<0,00001). This was confirmed by several studies [18]. Triple negative breast cancer often follows an aggressive disease course with poorer disease-specific survival compared to other breast cancer subtypes. Our study also confirmed the association of this phenotype with a high SBR grade and histological types of poor prognosis such as metaplastic carcinoma, infiltrating papillary carcinoma and poorly differentiated carcinoma.

SUMMARY

Our results seem to confirm that the prevalence of molecular subtypes is different depending on the ethnic group. Our population is in an intermediate zone between the aggressive basal-like cancers (African-American women) and the luminal A (Western and European population) of very good prognosis.

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