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ORIGINAL ARTICLE

Atypical hyperplasia and invasive Breast Carcinomas: clinical-morphological and biological study of 69 cases diagnosed in Oran

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ABSTRACT

Breast cancer is the most common cancer in women. It accounts for more than a third of all new cases of cancer. Its therapeutic management and the appreciation of tumor aggressiveness are based on the study of the clinical-morphological and biological characteristics of the patient and the tumor. Hyperplasia is a relative histological risk factor of 4 to 5 to develop invasive carcinoma. Our study is prospective comparative whose main purpose is to determine and compare Clinico-morphological and biological features of tumors associated and not associated with atypical epithelial hyperplasia. We have implemented histology and immunohistochemistry techniques. Patients with infiltrating carcinoma associated with hyperplasia represent 52.2% of the general population with a mean age of : 46.06 ± 10.9 years, 64% of premenopausal patients. 62.4% of tumors are pT1, 53.1% infiltrating ductal carcinoma (DIC), 80% SBRIII; 74% pN +, 72% RE-, 72% RP-, 83% HER2 +, 63% Ki67+, the HER2 molecular subtype is predominant. Patients with infiltrating carcinomas not associated with HEA represent 47.8% of the general population with a mean age of : 52.25 ± 8.98 years, 62.5% of peremenopausal patients, 50% of tumors are pT2, 46.9% DIC, 100% SBRI, 67% pN-, 86% without capsular burst, 60% RE +, 55% RP +, 64% HER2-, 60% Ki67-, the luminal molecular subtype is predominant. In our study, there is a relationship between the association of the tumor with the HEA and the expression of the characteristics of tumor aggressiveness.

Key words: *invasive carcinoma, atypical hyperplasia, hormone receptors, HER2, tumor aggressivenes.*

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INTRODUCTION

Breast cancer is the first cancer diagnosed in women in Algeria. It is at the head of mortality. Its incidence continues to increase year by year by 7% [1]. The development of most breast cancers occurs over long periods in a multi-step process starting with flat epithelial lesions leading to invasive cancers going through atypical hyperplasias and carcinomas in situ [2].

Atypical hyperplasias (intraepithelial lobular neoplasia, flat atypia, atypical ductal hyperplasia) are borderline lesions. If hyperplasia is not a form of breast cancer, it has characteristics that recall the early stages of the disease. It is not only a histological risk factor for secondary cancer but also a risk marker for concomitant Neighborhood cancer [3].

There are different types of morphological, immunohistochemical and molecular biology arguments to evoke tumor affiliation between atypical hyperplasia and carcinoma in situ and invasive. Moreover recent results of genetic studies show that alterations found in DCIS or invasive cancers are already present in the HEA [4].
The main objective of this study is to describe and compare the features clinico-morphological and biological of invasive breast carcinomas associated with HEA and those of invasive breast carcinomas not associated with the HEA to demonstrate whether there is a relationship between the combination of the tumor to the HEA and expression of poor prognostic features.

MATERIAL AND MATHODS

This is a comparative descriptive study realized from 1st January to 30 th June 2016 involving 77 patients with breast cancer after clinical, radiological and histological diagnosis.
The analysis of the samples was carried out at the Laboratory of Developmental Biology and Differentiation in collaboration with Dr. Korso's cytology and pathological anatomy laboratory. The cases were selected on the basis of a pathological diagnosis of invasive primary tumors confirmed after proofreading blades by two different pathologists. After informed consent, all patients who received neo-adjuvant therapy were excluded from the study and any tumor classified HER2 score 2. For each patient included, a questionnaire was established to collect clinical parameters (age, hormonal status), morphological parameters (PTN, histological type, SBR, presence or absence of atypical hyperplasias) and biological parameters (tissue markers ER, PR, HER2 and Ki67).
Two routine techniques were implemented : the histological technique and immunohistochemistry. Samples selected for the study were fixed in diluted buffered saline formol then embedded in paraffin. For Hemalun Eosine staining, 5µ slices were made. After identification of the infiltrating component, 3µ sections were made on silanized slides for the immunohistochemical study. DAKO products have been used: monoclonal antibodies: ER : (clone 1D5 DAKO code 1575 ref. PDM001-01) , PR : (Pg R 636 DAKO code 1630 ref M3569), Ki67 (MIB-1) : (clone SP6 ref. RMAB004) and a polyclonal HER2 antibody.
Data from the technical sheet was collected on the SPSS 20 software after creating an input mask. As all data is qualitative or quantitative discontinuous the Khi2 test was calculated in search of relations between the different parameters with $p < 0.05$ considered statistically significant.

RESULTS

1- description of the general population :
During the study period, 77 female patients with primary breast cancers were diagnosed including 69 infiltrating carcinomas were selected for the study of the association of atypical hyperplasia and comparisons.
The average age of the 69 patients selected is 49.43 ± 10.65 years , with a predominance of the age group 45-55 years.
Patients included in the study are predominantly premenopausal (72%), the most common histological type was invasive ductal carcinoma (71%) and predominance of SBR II grade (77%).
The lymph node status is positive in 55% of invasive carcinomas ,34% of which is capsular break. An almost equal distribution is observed for stages of lymphadenopathy pN0, pN1, pN2 (17%, 29% and 26%). In 28% of the stadium has not been determined (PNX). Tumors represent ER overexpression in 64% and overexpression of PR in 74%. For the HER-2 oncoprotein and the Ki 67 proliferation index, tumors are 35% HER-2 positive and 49% Ki 67 ≥ 15% (Ki 67+).
Tumors are subdivided according to molecular subtypes into: 57% luminal A, 29% luminal B, 4% luminal indeterminate (HER-2 score 2), 6% HER-2 and 4% triple negative.
The comparison of these different variables between the group of subjects with breast carcinoma associated with HEA and the group of subjects with breast carcinoma not associated with HEA showed a statistically significant difference associated with : age, SBR grade, lymphadenopathy, capsular intrusion, overexpression of RE, RP, HER-2 and Ki67.
2- description and comparison of the clinical and biological characteristics of tumors associated with HEA and those not associated with HEA:
All clinical and pathological characteristics of patients and tumors are shown in "Table 1".

Table 1: clinical and pathological characteristics of patients and tumors associated and not associated with atypical epithelial hyperplasia:

Characteristics	**The total series (N= 69)**		**Subgroup I CI with AEH (N=36)**		**Subgroup II CI without AEH (N=33)**		**P value**
	No. of patients	**%**	**No. of patients**	**%**	**No. of patients**	**%**	**P**
Average age (years) Median Stretch	49.07±10.42 49 74 - 27		46.06 ± 10.9 46 62-27		52.25 ± 8.98 52 74-32		
Age groups 25-35 35-45 45-55 55-65 65-75	 8 17 24 16 3	 11.50% 24.60% 34.80% 23.20% 3%	 7 9 9 10 0	 87% 52.94% 37.5% 62.5% 0%	 1 8 15 6 3	 13% 47.05% 62.5% 37.5% 100%	0.013
Hormonal status Menopaused Premenopausal Non-menopausal	 19 24 25	 28% 35% 37%	 10 9 16	 52.6% 37.5% 64%	 9 15 9	 47.4% 62.5% 36%	0.178
Histological types IDC IDCcomedo. IDC polymorp. ILC Mucouscolloid C. cribri. C. / Phyllod T. Paget's disease	 49 3 10 2 3 1 1	 71% 4% 15% 3% 4% 2% 1%	 26 2 7 0 0 0 1	 53.06% 66.6% 70% 0% 0% 0% 100%	 23 1 3 2 3 1 0	 46.9% 33.3% 30% 100% 100% 100% 0%	0.018
Tumor size Tx T1 T2 T3	 7 29 30 3	 10% 42% 44% 4%	 - 18 15 2	 - 62.06% 50% 66.6%	 - 11 15 1	 - 37.93% 50% 33.3%	0.34
SBR GRADE I II III	 1 53 15	 1% 77% 22%	 0 24 12	 0% 45.28% 80%	 1 29 3	 100% 54.71% 20%	0.034
Lymphnodestatus PNx PN- PN+	19 12 38	28% 17% 55%	- 4 28	- 33.3% 73.68%	- 8 10	- 26.3% 26.31%	0.00
Invasive Lymphnode stage PNx PN0 PN1 PN2	19 12 20 18	28% 17% 29% 26%	- 4 15 13	- 33.3% 75% 72.22%	- 8 5 5	- 66.6% 25% 27.7%	0.001
Capsular effraction WithCapsul. Effrac. With outcapsul. Effrac.	13 25	34% 66%	11 17	84.6% 68%	2 8	15.38% 32%	0.00

ER Status ER+ ER-	 44 25	 64% 36%	 18 18	 40.9% 72%	 26 7	 59.09% 28%	0.013
PR Status PR+ PR-	 51 18	 74% 26%	 23 13	 45.09% 72.22%	 28 5	 54.9% 27.77%	0.048
HER2 Status HER2+ HER2-	 24 44	 35% 65%	 20 15	 83.33% 34.09%	 4 29	 16.66% 65.9%	0.00
Ki67 Status <14% ≥14%	 35 34	 51% 49%	 14 22	 40% 64.7%	 21 12	 60% 35.29%	0.04
Molecular subtypes Luminal A Luminal B HER-2 Triple négatif (Basal like) Indéterminé	 39 20 4 3 3	 57% 29% 6% 4% 4%	 16 16 4 0 0	 41.02% 80% 100% 0% 0%	 23 4 0 3 3	 58.97% 20% 0% 100% 100%	0.001

DISCUSSION

Our prospective study involved 77 women with breast cancer ; the mean age of our series of patients was 49.43 ± 10.68 years with a median of 49 years. The age group with the highest number of cases is 45-55 years old. Abbass in Morocco [5] reported an average age and a median of 45 years. Ben Ahmed in Tunisia [6], Alkhateeb and Abd in Iraq [7] have shown that the average age of women with breast cancer is 50 years with a peak frequency between 41 and 50 years.

Taking into consideration the presence and absence of atypical hyperplasias, the distribution of patients by age changes,that of the group of patients with infiltrating carcinoma (IC) associated with atypical hyperplasias (AH) are younger (median = 46 years) similarly for the age range that for the same group extends between 27 and 62 years. According to the data of Antoine et al [2], the young age of women is a very powerful argument that confirms the tumor affiliation between atypical hyperplasia and infiltrating carcinoma since the average age of women with atypical lesions is younger than the average age of carcinoma in situ and that of invasive carcinoma. This association of HEA with invasive carcinoma can only be explained by the rapidity of the malignant transformation of cells in one subject compared to the other.

Before the menopause the prognosis is even worse than the patient is young, after menopause the risk of death from cancer increases after age 70 [8]. This excess mortality after 70 years may be due to the normal reduction in life expectancy with age [9].

In our study a predominance of non-menopausal and pre-menopausal patients is recorded whether for the first group (IC with AEH) or the second group (IC without AEH), these results are in agreement with the study of Espié *et al* [10], who suggested that a RR of 1.4 to have breast cancer is noted for the patients who are still regulated compared to those who are not. The results of another study by Alexander and Roberts [11] report that subclinical tumors pre-exist in rapid and accelerated growth when subjected to pre-menopausal ovarian hormone levels.

In our series, the distribution of tumors studied according to the histological type showed a large majority of infiltrating ductal carcinomas (IDC). Other invasive forms are rarer. These data are consistent with that of Alkhateeb, Kotsopoulos, Van Der Hage, Bennani and Lamy *et al* [7,13,9,12,14]. The distribution of the two subgroups according to the histological type is almost equal for the non-specific IDC type. However, the group of tumors associated with AEH record high frequencies for comedocarcinoma and polymorphic IC types with 66.7% and 70%, respectively, which are good-prognosis carcinomas, on the other hand, Paget's disease, which has a very poor prognosis, is only recorded in this group. These results are consistent with those of Abdel Fatah al [15] have shown that pre-invasive lesions of atypical ductal metaplasia (MCA), atypical ductal hyperplasia (CAH), atypical lobular hyperplasia (HLA) and lobular

carcinoma in situ (CLIS) are generally associated with well-differentiated carcinomas of the invasive tubular, tubular lobular and lobular carcinoma type. Our series shows a statistically significant difference between the infiltrating tumor association with HEA and SBR grade. 45% of grade II tumors and 80% grade III tumors are associated with atypical hyperplasias, whereas no tumors of this group are grade I. SBR grading is an important prognostic factor that can determine the correlation between the morphological aspect of a tumor and its degree of malignancy [16] ; the higher the grade, the higher the tumor is aggressive and the prognosis is poor. Tumors associated with the AEH in our series have high grade SBR giving it a significant aggressiveness therefore a worse prognosis. Alkhateeb and Abd reported similar results by studying the correlation between the histological grade of breast cancer and lymph node involvement in 130 patients in Iraq [7]. Our results also agree with those of Shahid Siddiqui *et al* (2016) and Rakha *et al* (2016) who have demonstrated in their studies that a high histopronotic grade is associated with a poor prognosis [17, 18].

The axillary nodes involvement is for now the most important prognostic factor for predicting local recurrence after conservative treatment and distant relapse [19]. The overall 10-year survival passes from 79% for patients called pN- to 47% for patients called pN + [35].In our study, lymph node involvement (pN +) was observed in 55% of patients with 74% of these are patients with invasive carcinoma associated with hyperplasia with a predominance of pN1 and pN2 versus 26% lymph node involvement observed in the group of patients with invasive carcinoma without AEH. Different results are reported by Khudair *et al* (2016) and Yalda (2013) whose nodal involvement with these stages is recorded with lower frequencies [20, 21]. Our results are similar to studies conducted in Morocco by Bennani (2016), in Iraq by Alkhateeb and Abd (2016) and in the Netherlands by Van Der Hage (2011) [9, 7, 13].

There is an established relationship between lymph node involvement and tumor size and prognosis the size of the tumor is classified among the most powerful predictors of distant metastasis and overall survival after adjuvant. Our results show a predominance of T2 size with 44%. Al-khafaji (2016), Alkhateeb (2016), and Abdullateef (2015) recorded similar frequencies in their studies of different populations in Iraq [22, 7, 23]. Bennani suggested that an increase in tumor size in the Moroccan population was associated with a poor prognosis [9].

The immunohistochemical study allows the detection of the biological or molecular factors constituting the new prognostic factors determining the therapeutic arsenal [24]. The biological markers that are systematically sought are the hormonal receptors: estradiol (ER), progesterone (RP) and HER2 oncoprotein receptors.

Tumors overexpressing RE and / or RP are likely to respond to antihormonal treatment. The response to this treatment is associated with a good prognosis [25]. PRs are induced by ERs, so they would reflect functional REs, they are not always taken into account in therapeutic decisions. They are important for the diagnosis of triple negative and luminal B subgroups. Their prognostic value remains controversial [26].

In our series, the ER status is mostly positive for the general population (64%) dominated by tumors not associated with hyperplastic lesions with 60%. By cons, tumors associated with hyperplastic lesions are in most cases ER negative (72%). this marking difference is statistically significant. almost the same significant frequencies are recorded for progesterone receptors (RP). Our results agree with those of Suhad Faisal (2016), Abdullateef (2016), Khudair (2016) and Solomon (2012) [27, 23, 20,26]. But taking into consideration the presence of hyperplastic lesions, our results opposed to those of the study by Luciene et al (2006) who found overexpression of ER and RP in mammary tumors associated with atypical hyperplasia in 94% and 97% of cases respectively [28]. Also, for the negative ER cases, they noted a slight expression of these receptors in epithelial cells of atypical hyperplasias only. Other studies have reported a heterogeneous expression of ERs in epithelial cells of atypical hyperplasias, This heterogeneity of expression is linked to an intense proliferative power which is the consequence of an increased rate of spontaneous mutation; the origin of the polyclonal profile of tumors [29, 30].

The overexpression of the HER 2 / neu protein has become an indispensable prognostic and predictive marker [14]. A significant link between amplification / overexpression of HER2 and pejorative evolution with increased recurrence after treatment and decreased survival [31]. The search for the overexpression of HER2 oncoprotein has become a routine examination for all invasive tumors since it conditions treatment with a targeted therapy (treatment with Trastuzumab) [32]. 35% of the infiltrating carcinomas included in our study overexpress HER2 oncoprotein. Similar results are reported by Abdullateef *et al* (2016), Van Der Hage (2011), Suhad Faisal (2016) and Khudair *et al* (2016) who found HER2 overexpression of, 13.7%, 26%, 26% and 16% respectively [23, 13, 27,20]. Other studies have shown different results, Salomon (2012) reports an HER2 overexpression rate of 76% [26]. 83% of the HER2-

positive tumors in our series are infiltrating carcinomas associated with hyperplasia, which is a poor prognostic indicator. According to Antoine *et al* [2], a HER2 gene amplification and overexpression of the corresponding protein are characteristic of high grade lesions and therefore of poor prognosis.
The Ki-67 is a marker of cell proliferation alternative to the mitotic index of SBR grade, it detects a nuclear antigen present during the entire cell cycle except the quiescent phase G0 [14, 16]. Overexpression of Ki-67 is associated with a poor prognosis. Our series of infiltrating carcinoma shows an expression of Ki-67< 14% in 51% of cases (Ki-67 negative), these values are similar to those described by Luciene *et al.* [28] who found a negative expression of Ki-67 in 64% of tumors, and are the opposite of Khudair's results, which found positive expression (Ki-67≥14%) in 69% of cases [20]. Considering the combination of atypical epithelial hyperplasia to invasive carcinoma, this group strongly expresses the Ki-67 antigen, which confirms the evolutionary and aggressive profile of this group of tumors.
The study of the frequency of molecular subtypes revealed a predominance of luminal tumors with 57% luminal A, 29% luminal B. the other types are minority with 6% of tumors HER2 + and 4% basal like. Our results agree with those of Van Der Hage *et al* [13] Faisal and Suhad *et al* [27]. Other studies have demonstrated a predominance of luminal B subtypes [33, 34]. Our study shows a highly significant difference between the association of invasive carcinomas with AEH and the luminal B and HER2 + subtypes. This non-homogeneous distribution of molecular subtypes appears to be due to the limited number of cases studied (69 cases).

CONCLUSION

Our results show that the invasive breast carcinomas associated with atypical epithelial hyperplasia (HEA) include poor prognostic features, which leads us to suggest a specific management of this type of lesions.

LINKS OF INTEREST

The authors have declared that no competing interest exists**.**

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