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Original

Triple Negative Invasive Breast Carcinoma: Incidence and Clinical - Pathological Characteristics

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Abstract

Aim: The epidemiological behavior of malignant tumors in Costa Rica has undergone an important change during the last years; breast carcinoma has increased its incidence, occupying the second place in malignancies in women and the first one in mortality. This type of tumor can be studied by several immunohistochemistry markers, such as the expression of different hormonal receptors by neoplastic cells (estrogen receptors, progesterone receptors and Human Epidermal Growth-Factor Receptor type 2, HER2). Carcinomas which do not express any of these three receptors have a worse prognosis. Objectives for this study were to determine the main characteristics of these tumors, named triple negative carcinomas, and to define their relevance within breast carcinomas.

Methodology: Data was collected from all women with breast cancer diagnosed, with immunohistochemistry studies, from January 1st, to December 31st, 2006, at the Pathology Department of the San Juan de Dios Hospital. Patient´s age, histological type and degree of differentiation, were taken into account for each case. Triple negative carcinomas were considered separately, and statistical analysis was made with Epi Info 3.3.4 software.

Results: During the above mentioned period, 221 patients were diagnosed with breast cancer, 40 of them were identified as having triple negative carcinomas, which meant an incidence of 18% (C.I. 95%, 12.79 – 23.40), and had an average of 54 years old (C.I. 95%, 50 - 58), a median of 52 years old and a mode of 48 years old. Triple-negative cancer was more related with ductal infiltrating histological type: 67.5% (C.I. 95%, 51.73-83.26), followed by infiltrating lobular, with 12.5% (C.I. 95%, 4.18 – 26.80), medullary, with 5%, and less related are papillary type and spindle cell metaplastic carcinoma. According to the degree of differentiation, there were 23 grade-3 cases, 8 grade-2 cases,
and 3 grade-1 carcinomas.

Conclusion: Triple negative breast cancers are an aggressive group of tumors, which manifest at younger ages, have larger tumor size, are of higher histological grade, and mostly are infiltrating ductal carcinomas. Due to the fact that this was based only on determination of hormonal receptors and HER2, other tests might be necessary such as CK5/6 and 17 stains to check basal-like carcinoma cases. Also, this study shows a higher prevalence for infiltrating lobular carcinomas than other studies, so that other tests could be done such as e-cadherin, to verify the cases of lobular carcinomas, thereby increasing reliability of results.

Keywords: breast cancer, triple-negative, immunohistochemistry, progesterone and estrogen receptors, Human Epidermal Growth-Factor Receptor type 2 (HER2).

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Abbreviations: TNBC, Triple Negative Breast Carcinoma; HER2, Human Epidermal Growth-Factor Receptor Type 2; CK, cytokeratins; HSJD, San Juan de Dios Hospital.

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Breast cancer constitutes a public health issue in Costa Rica[1]. There is an increasing tendency of new breast cancer diagnoses, from a 30.28 cases per 100000 women rate in 1996, to 40.07 cases per 100000 women in 2003.[1]

Breast cancer has been classified from different points of view,[2, 3] such as the histological classification, which has made possible to determine two different groups: carcinoma *in situ* and invasive carcinoma. Invasive breast carcinoma penetrates the basal membrane into the mammary stroma, where it can invade blood vessels, regional lymph nodes and allow distant metastasis;[2] these invasive types represent 70% to 85 % of carcinomas, and mostly are ductal invasive cancers.[2]. Among the main breast carcinoma histological types, we can identify ductal carcinoma (79%), lobular carcinoma (10%), tubular carcinoma (6%), mucinous carcinoma (2%), papillary carcinoma (1%) and metaplastic carcinoma (1%).[4, 5]

Another breast carcinoma classification uses immunohistochemistry markers, which allow detecting cell proteins, [4] and has led to the categorization of breast carcinomas according to their expression of estrogen receptors, progesterone receptors, and Human Epidermal Growth-Factor Receptors type 2, HER2.[4, 5]

Nearly 75% to 80% of breast cancers are positive for hormonal estrogen or progesterone receptors, and 15% to 20% are HER2 positive. The remaining percentage from 10% to 15% represents Triple Negative Breast Carcinomas (TNBC), defined as the absence of hormonal and HER2 receptors expression (Figure 1). According to gene expression, breast carcinomas are divided into five groups. [6-8] (Figure 2).

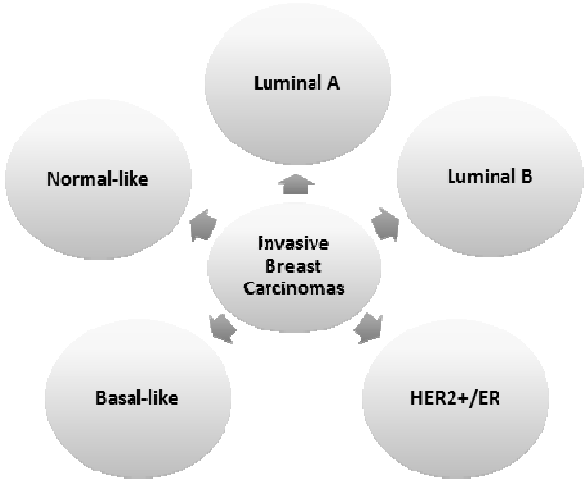

Figure 2. Invasive breast carcinoma types

About 85% of TNBC´s are identified as basal-like carcinomas on immunohistochemistry studies; basal-like carcinomas are triple negative, but not all triple negative carcinomas are basal-like.[8] These basal-like carcinomas are negative for estrogen receptors, progesterone receptors and HER2; on the other hand, such carcinomas are positive for staining with myoepithelial cytokeratins or basal cells CK 5/6 and 17. It is assumed that these tumors have their origin at the external or basal layer of the mammary ducts (myoepithelial cells), hence the name. [8] (Figure 3).

This type of breast tumor (basal-like) is more common in premenopausal women, African-Americans or Hispanics, and of lower socio-economic status; they´ve been associated with aggressive histologic characteristics, bad prognosis, and a shorter survival than other breast cancers on the same stage, and they also have been related

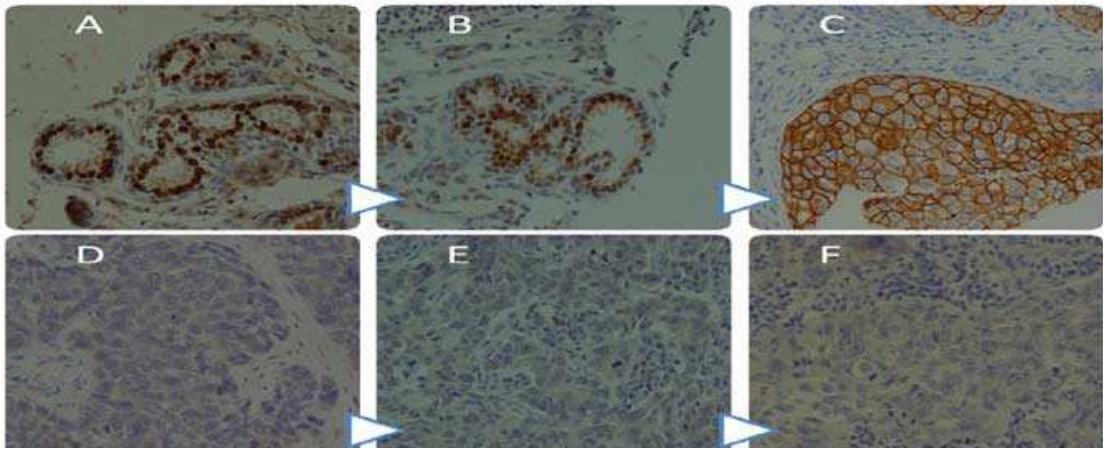

Figure 1. Breast cáncer with immunohistochemistry receptor markers for: a) Progesterone, b) Estrogens, c) HER2, d,e and f) Negative

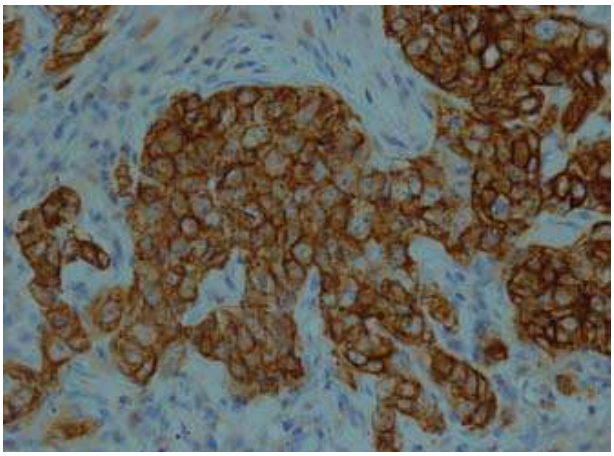

Figure 3. CK5 Immunohistochemistry on breast cancer

As a result of the above characteristics, this entity is resistant to hormonal treatments and other actions, this because it doesn´t express the required proteins for the treatments to work.[8] A neoplasia positive for estrogen receptors predicts that it will respond to endocrinologic treatment with anti-estrogenic drugs such as tamoxifen or ovarian suppression.[10] In like manner, a tumor positive for HER2, is eligible for treatment with specific target-oriented drugs such as monoclonal antibodies against HER2 (trastuzumab).[10]

Materials and methods

The study included all women with breast cancer diagnosis, confirmed in biopsies with immunohistochemistry studies (estrogen receptors, progesterone receptors, and HER2) at the Pathology Department of the San Juan de Dios Hospital (HSJD), on the period from January 1st to December 31st 2006.

This is an observational, retrospective, descriptive and transversal study. Variables analyzed were the following: biopsy number; histologic grade; size; surgical margins; calcifications; nervous, vascular or lymphatic invasion; nodal invasion and staging. When necessary, the patient´s file was revised to complete data.

Analysis and description of variables were made; for quantitative variables, by estimation of measures for central tendency and dispersion; and for qualitative variables, by determination of frequencies and proportions. The different groups were described according to the presence of hormonal receptors or not. Characteristics from each of these groups were compared with the control group (without receptors), by the "t student test" for quantitative variables, and by the "Chi square test for homogeneity" for qualitative variables. The value 0.05 was defined as a statistically significant critical point ($a \leq 0.05$) for all statistic tests. Analyses were made with Epi Info 3.3.4 (CDC-2007) and using an exportable to Epi Info Excel worksheet.[11]

This study was approved by the Local Research Bioethics Committee, at HSJD (CLOBI-HSJD-023-2008).

Results

The study found 221 patients with invasive breast carcinomas, during the mentioned year, at the Pathology Department of HSJD. According to this total number, TNBC diagnoses incidence rate was calculated for 2006 on HSJD: 18 per 100 women (C.I. 95%, 12.79-23.40) (Table 1).

The average age for patients with TNBC was 54 years old (C.I. 95%, 50-58), with a 52 years old median, a mode of 48, and standard deviation of 13.46.

TNBC was more related to ductal infiltrating histological type in 67.5% (C.I. 95%, 51.73-83.26), followed by invasive lobular carcinoma with 12.5% (C.I. 95%, 4.18-26.80), medullary in 5% (C.I. 95%, 0.61-16.92), and less related to papillary carcinoma, with 2.5%, and spindle cell and squamous cell metaplastic carcinomas, also with a 2.5% (C.I. 95%, 0.06-13.16). We must clarify that in one case, it wasn´t possible to obtain the TNBC histologic type (Table 2).

Table 1: Breast cancer classification according to receptor expression

Receptors	N	%
HERII (-) / RP (+) / RE (+)	122	55.2
HERII (-) / RP (-) / RE (-)	40	18.1
HERII (-) / RP (-) / RE(+)	19	8.6
HERII (+) / RP (-) / RE (-)	17	7.7
HERII (+) / RP (+) / RE (+)	12	5.4
HERII (+) / RP (-) / RE (+)	8	3.6
HERII (-) / RP (+) / RE (-)	3	1.4

Table 2: Histologic types for triple negative breast carcinomas in HSJD

Histologic type	N	%
Ductal Infiltrating	27	67.5%
Lobular Infiltrating	5	12.5%
Infiltrating Intraductal	3	7.5%
Medullary	2	5%
Papillary	1	2.5%
Spindle cell and squamous cell metaplastic	1	2.5%
Not reported	1	2,5%

In regard to TNBC´s histological grade, there were 23 grade-3 cases in HSJD, 8 grade-2 cases and 3 grade-1 cases, taking into account that 6 cases didn´t have reported histological grade, which reflects that TNBC presents with high histological grades. Agreeing with the above, out of the ductal infiltrating carcinoma cases reported (27 cases), 17 were histological grade 3 (62.9%) (Table 3).

Table 3: Distribution of triple negative breast carcinomas according to tumor size

Tumor size	N	%
≤ 2,0 cm	16	40%
2cm – 5cm	18	45%
> 5cm	4	10%
Not reported	2	5%

Between the TNBC cases studied, 12 had nodal metastasis, and 6 had compromised margins, those 6 were ductal infiltrating carcinomas.

Discussion

Regarding to TNBC´s age at diagnosis in the studied population, agrees with data mentioned in literature, as well as research data from different populations. For example, a TNBC study made in California, USA, determined that the median age for this cancer´s diagnosis was 54 years old.[9] This is of great importance, because TNBC affects women at much younger ages than other types of breast cancer.

TNBC in this study represented 18% of breast cancers detected in that year. This is a higher frequency than the one mentioned in the literature, of 15%,[8] and than the frequency reported in the California study, of 12.5%. Such difference could be explained by two main reasons: different genetics of the studied populations, or false negatives originated by sample handling.

Some problems in tissue fixation can occur with sample handling,[12] which leads to a higher false negatives percentage for hormonal receptor tests, thereby showing a higher incidence of TNBC.

In another study realized at the Pathologic Anatomy Department of HSJD, about the extraction of amplifiable DNA fragments, extraction was achieved in less than 50% of samples, which is considered low, and is a fact that could derive a variation in epitope conservation, which also could affect immunohistochemistry tests.[12] Such data should be considered when analyzing the frequency of these triple negative tumors.

Reported, in frequency order of infiltrating TNBC, are: ductal (68.4%-86%), medullary (5.3%-5.8%), lobular (2.9%-1%), cribriform (0-0.9%), mucinous (0-2%), and papillary (0.6%-0.9%), these are similar proportions to the ones described in other studies,[13-15] with the exception of lobular carcinomas, with a higher prevalence in this study.

Concerning to histological grade, it is reported that more than half of the ductal carcinomas are poorly differentiated,[13-15] which agrees with our study, where 62.9% of ductal triple negative carcinomas were poorly differentiated.

It is alarming that regarding tumor size, more than half of TNBCs were larger than 2 cm, which is related to late diagnosis. [9]

TNBCs are a group of aggressive tumors, which manifests at younger age, with larger size, with higher histological grade, mostly are infiltrating ductal carcinomas, and in Costa Rica they have a higher incidence than other places.

Because this study was based only on hormonal receptors and HER2 tests, other tests could be realized such as CK5/6 and 17 stains to confirm basal-like carcinoma cases. Also, this study shows a higher prevalence for infiltrating lobular carcinomas than other studies, so that other tests could be done such as e-cadherin, to verify the cases of lobular carcinomas, thereby increasing reliability of results.

Basal-like type breast cancer is an important entity that should be studied, because of its particular characteristics compared with other breast cancer types. A pending essential step in this country is to determine triple negative mammary tumors corresponding to basal-like type carcinomas.

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