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Analyzing the clinical-pathological characteristics of HER-2 ultra-low breast cancer in a medium-sized Brazilian city: a brief communication

Analisando as características clínico-patológicas do câncer de mama HER-2 ultra-low em uma cidade brasileira de médio porte: uma comunicação breve

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INTRODUTION

The Cancer National Institute estimated 74,000 new cases of breast cancer between 2023 and 2025.[1] In terms of global data, breast cancer is the most common cancer among women, with 2.3 million new cases (24.5%).[2]

In 2013, the St. Gallen International Breast Cancer Conference have categorized breast cancer into four estimated molecular subtypes based on them prognosis, viz. Luminal A, Luminal B, triple-negative (TNBC), and human epidermal growth factor receptor 2 positive (HER2+).[3]

The HER-2+ breast cancer is classified when its expression is 3+ by immunohistochemistry (IHC) or 2+ IHC with gene amplification by molecular studies. Among non-amplified tumors there are three possible categorizations. HER-2- completely negative is defined when there is no membrane reaction. Low HER-2 is defined with IHC marking 1+ or 2+ with no confirmed amplification. Finally, HER-2 ultra-low expression was defined as invasive cells showing at least ≤10% membrane protein staining or incomplete weak membrane staining.[4-6]

Tuhulong et al[7], Shi et al[4], and Chen et al[8], are the only worldwide studies describing the clinical-pathological characteristics of HER-2 ultra-low breast cancer.[4,7,8] There are no Brazilian studies on the subject. Therefore, the importance of this short communication is to describe the clinical-pathological characteristics of this group of breast cancer in a Brazilian middle city which can help to stablished new public health strategies.

METHODS

This was an observational, retrospective, quantitative study based on data from a pathology service located in the countryside interior of the State of São Paulo, Brazil.

In this research, pathology reports obtained through biopsy or surgical excision in the period between January 1, 2017 and June 30, 2020 (42 months) were included and reviewed. All cases of Her-2 ultra-low breast carcinoma ultra-low were analyzed because de aim of this study was to analyze the clinicopathological characteristics of this type of tumor exclusively. Papillary carcinomas were excluded from the study due to the complexity of this tumor subtype.

In the included population, age, histologic subtype and immunohistochemical data for the estrogen receptor, progesterone receptor and KI-67 (<20% x ≥20%) were assessed.[4,7,8] The data was evaluated by two pathologists, following the recommendations for immunohistochemical tests of following the recommendations for immunohistochemical tests of estrogen and progesterone receptors in breast cancer.[9]

Paraffin samples were subjected to immunohistochemistry for Estrogen Receptor (ER) (Clone: EP1; prediluted ready-to-use) Progesterone Receptor (PR) (Clone: PgR636; prediluted ready-to-use) HER-2 (Clone: Polyclonal, dilution 1: 200) and Ki-67 (Clone: MIB-1; pre-diluted ready-to-use) according to the Dako®

Immunhistochemistry Autostainer Plus manufacturer's protocols. There were positive and negative internal and external controls. These protocols are according to the recommendations of American Society of Clinical Oncology/College of American Pathologists.[9] Sections were analyzed by two pathologists who defined the level of positivity of the markers based on the most current review that discusses the various cut-off points.[10] Cases were subjected to approximate molecular classification following the WHO classification.[4]

Statistics Analysis was carried out using Microsoft Office Excel version 2016. Absolute and relative frequencies (%) and standard deviations (SD) of the results were calculated.

The Research Ethics Committee of our institution approved the study with acceptance number CAAE: 36593120.0.0000.5379 and approval number 4365915. Written informed consent was waived due to use of anonymized existing medical material or data and the retrospective study design.

RESULTS

A total of 52 samples from women diagnosed with Her-2 ultra-low breast cancer were analyzed. The sample is practically divided in half between biopsies and excisions. Age ranged from 34 to 93 years old (mean: 60 years; SD: 16,28).

The majority of the sample was positive for estrogen and progesterone receptors (88,4 and 78,8% respectively). Only 11 samples were below the cut-off for the KI-67 marker (SD: 21,1). In terms of histological subtype, ductal carcinoma was the most prevalent. Further data on clinical-pathological characteristics of Her-2 ultra-low breast cancer can be found in Table 1.

DISCUSSION

The analyzed population has a high advanced age and tumors showing positivity for estrogen, positivity for progesterone receptors and high levels of the KI-67. Ductal carcinoma was the predominant subtype. Which is in agreement with the current global epidemiology of breast cancer proposed by World Health Organization (WHO).[11]

Table 1: Distribution of immunohistochemical markers and histologic subtype.

HER-2 ultra-low		
Estrogen receptor	Positive	46 (88,4%)
	Negative	6 (11,6%)
Progesterone receptor	Positive	37 (71,1%)
	Negative	15 (28,9%)
KI-67	<20%	11 (21,2%)
	>=20%	41 (78,8%)
Ductal	44 (84,7%)	
Lobular	4 (7,7%)	
Metaplasic	2 (3,8%)	
Mucinous	2 (3,8%)	

In recent years, there has been a growing number of studies addressing the clinicopathological characteristics of HER-2 low. On the other hand, there are not many studies that address the same characteristics of the ultra-low. Only three studies were found in the world literature describing some clinicopathological characteristics of HER-2 ultra-low breast cancer.[4,7,8]

Tuluhong et al[7], evaluated 85 cases of HER-2 ultra-low in patients diagnosed with breast cancer and undergoing surgery from 2008 to 2019 in a Chinese hospital. Regarding age, 57 patients were over 50 years old (67% of the sample). Hormone receptors were positive in 63 patients (40 of the over 50 years old) and negative in 22. The individual estrogen and progesterone receptor positivity is not reported in the study. The cutoff used in this study for Ki-67 analysis was 14%. Most patients were above the cutoff (55 patients).[7]

Shi et al[4], evaluated 1024 patients diagnosed with HER-2 ultra-low breast cancer during the entire period of 2018 at a Chinese university hospital. Most patients were under 55 years old at the time of diagnosis, representing approximately 58,2% of all patients. Regarding immunohistochemical receptors, the estrogen receptor was positive in most of the sample (182, 73,1%). The progesterone receptor was also positive in most cases (162, 67,4%).[4]

Chen et al[8], described 395 patients diagnosed with HER-2 ultra-low breast cancer from January 2018 to December 2019 in an affiliated hospital of a Chinese university. Median age was 51 years old and media between 52-53. Ductal carcinoma represents 331 patients (83,8%). Hormone receptors were positives in 83% of cases. Media of Ki-67 was 15,6.[8]

Considering the previously described studies, there was a mild variation about age. In all populations, most of the tumors were positive to ER an PR. In relation to cellular proliferative index (Ki-67), in agreement of the present data, most of cases presented high Ki-67. Chien et.al., were the only who described histologic subtypes of breast cancer HER-2 ultra-low.[8] Ductal carcinoma was the most prevalent histologic subtype in their study, as well as in our data. It is in agreement of the well-known epidemiology of breast cancer.

The data from this study have some limitations. It was carried out in only one institution and the sample used was small. However, there are only three studies describing the clinicopathological characteristics of HER-2 ultra-low tumors. Thus, there is worldwide limitation (not only in Brazil) about HER-2 ultra-low breast cancer cases. In this way, our data can help to consolidate such information in Brazil and in the world, in addition to

encouraging further research on the subject.

CONCLUSION

The results of this study showed the clinical and pathological profile of HER-2 ultra-low breast cancer in our population is similar to what was described by the WHO: positivity for estrogen and progesterone receptors, high levels of Ki-67 and predominance of ductal carcinomas. More studies are needed to provide the real epidemiology of of HER-2 ultra-low breast cancer in the Brazilian society. It is important to highlight this is the first study in our nation with this aim.

FOUNDING SOURCE

There was no founding.

CONFLICT OF INTEREST

Nothing to declare.

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