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Cancer Stem Cells in Breast Cancer

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Abstract **Case Report**

Breast cancer represents a real public health problem in Morocco with one of the highest rates of mortality. Cancer stem cells are a small subset of cells found in many types of malignancies, including breast cancer, they have a crucial role in carcinogenesis, progression, recurrences and therapeutic resistance. Our study aims to understand the characteristics of breast cancer stem cells that could explain the aggressive behavior of certain tumors, with an emphasis on CD326, as a biomarker for BCSC, hoping for new targeted therapies in the future.

Keywords: Breast cancer, Morocco, malignancies, carcinogenesis.

INTRODUCTION

Breast cancer represents a real public health problem. It is the most common cancer in Morocco, representing 19.8% of all cancers combined and ranking second in mortality. In view of a better understanding of the mechanisms which lead to recurrences, metastases and resistance to treatments, the scientific community has focused on the role of cancer stem cells and their involvement in these various processes. Cancer stem cells are a small subset of cells found in many types of malignancies, including breast cancer, they have a crucial role in carcinogenesis, progression, recurrences and therapeutic resistance.

Our study aims to:

- Gain a better understanding of cancer stem cells.
- Focus on the epithelial cell adhesion marker (EpCam or CD326) in as a biomarker of breast cancer stem cells.
- Determine the different histopathological, immunohistochemical and pronostic aspects of malignant breast tumors containing cancer stem cells and those lacking them.
- Look for a possible correlation between the presence of breast cancer stem cells and poor prognosis.

STUDY:

Our study aims to characterize breast cancer stem cells (BCSC) by immunohistochemistry using the biomarker CD326 (EpCam), and to highlight the histopathological, immunohistochemical, evolutionary and prognostic aspects of malignant breast tumors with CD326.

This is a retrospective study over a period of 12 months (from January to December 2019), involving 32 cases of breast caner, conducted in the Department of Pathological Anatomy along with the Radiation oncology Department of the Mohammed VI University Hospital Center of Marrakech.

CD326 expression was assessed by immunohistochemicalstaining, among our study, CD326 was expressed in 91% of breast carcinomas; its percentage varied between 0 and 95%, a predominance was noted for a moderate intensity. The overexpression of CD326, was scored using the standard scoring system (IRS> 4, was deemed as overexpression), 59% of breast cancers overexpress this biomarker.

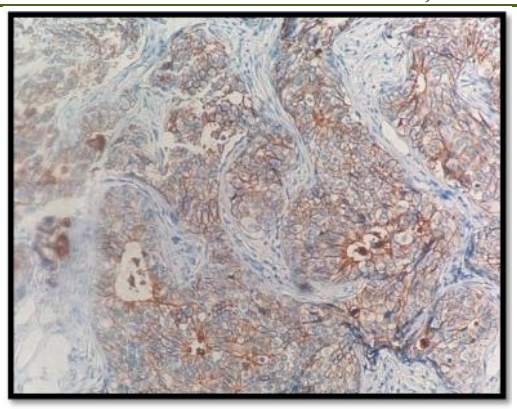

Figure 1: Example of a strong and complete membrane marking of breast tumor cells by the biomarker CD326

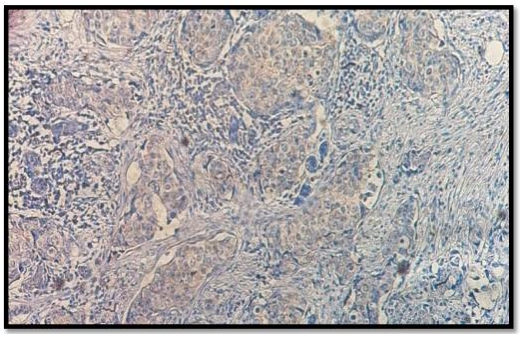

Figure 2: Example of a weak membrane marking of breast tumor cells by the biomarker CD326

There is an overexpression in patients aged over 50 (61%), as well as the patients in the premenopausal group (64%).

The ivasive ductal carcinoma overexpresses more of CD326 (62%) compared to the lobular and other histological types.

Regarding pathological tumor size, EpCam was overexpressed in 75% of pT4 tumors.

It was noticed that all triple negative breast cancers and HER2-enriched (100%) had an immunostaining score greater than 4. Moreover, the overexpression of CD326 has been observed in all (100%) of the negative hormone receptor status tumors, as well as in 67% of patients at the metastatic stage.

Table 1: Expression of the EpCam according to the evolution of the patients

	Nombre de patients	CD326 positif N (%)	CD326 négatif N (%)	Surexpression du CD326	
				Oui N (%)	Non N (%)
évolution clinique					
Bonne	19	17 (89%)	2 (11%)	11 (58%)	8 (42%)
Mauvaise	10	9 (90%)	1 (10%)	6 (60%)	4 (40%)
Contrôleloco-régional					
Bon	19	17 (89%)	2 (11%)	11 (58%)	8 (42%)
Mauvais	8	7 (87%)	1 (13%)	1 (100%)	0
Bilatéralisation	1	1 (100%)	0	1 (100%)	0
Lésions suspectes loco-régionales	2	1 (50%)	1 (50%)	0	2 (100%)
Autres aspects évolutifs					
Rechutes métastatiques	5	4 (80%)	1 (20%)	3 (60%)	2 (40%)
Décès	1	1 (100%)	0	1 (100%)	0
Perdu de vue	1	1 (100%)	0	1 (100%)	0

DISCUSSION

Historically, the emergence of the concept of cancer stem cells has first appeared in the 1990s when Bonnet demonstrated the ability to generate acute myeloid leukemia from a minority of cancer stem cells of the phenotype (CD34+CD38-) once injected into immunocompromised mice [1].

Subsequently, numerous studies have proven the existence of cancer stem cells in solid tumors, notably the breast thanks to the study of Al Hajj (2), but also in other locations (prostate, lung, skin…).
Breast carcinoma demonstrated heterogeneity according to:

- A hierarchical model, where only a fraction of tumor cells can self-renew [3].
- A a stochastic model, which is characterized by the potential of each cell, even when differentiated, to multiply tirelessly and consequently the constitution of new tumors [4].

Definition of Cancer Stem Cells:

Subpopulation of tumor cells with specific properties, very similar to normal mammary stem cells.

They have the capacity for self-renewal and multidirectional differentiation, thus playing a key role in tumor initiation, tumorigenesis, metastases, resistance to chemotherapy and tumor recurrence.

The characteristics of CSCS:

- Unlimited auto-renewal [6, 3, 7, 5].
- Plasticity: a fundamental characteristic of CSCS [8, 9].
- Tumor initiation capacity.
- Metastases.
- Radio and chemoresistance [10].
- The power to induce neovascularization [7].
- Resistance to apoptosis [8].

Breast cancer stem cell markers:

- CD44+ and CD24- cells have a strong capacity for invasion, migration and proliferation [11, 12, 13, 5, 14, 15].
- ALDH1, CD133, and EpCam are also correlated with the presence of CSCS [11, 16, 13, 5, 17].

Therapeutic consequences of the presence of CSCS:
Resistance to chemotherapy:

Zheng assert that CSCS induce resistance to several agents of chemotherapy in breast cancer [18], such as paclitaxel [19], anthracyclines [20], platinum salts and capecitabine [21, 22].

Resistance to hormonal therapy and targeted therapy:

Recent studies affirm the involvement of CSCS in resistance to tamoxifen, to anti-aromatases as well as Fulvestrant [21-23]. This resistance does not spare anti-HER2 agents, notably Trastuzumab and Lapatinib [21, 22, 24].

Resistance to radiotherapy:

Several studies report that in breast cancer, ionizing radiation is only effective on differentiated tumor cells, while CSCS survive because of their resistance to radiation therapy [25-27]. Their proliferation rates would increase, even significantly, after a post-radiotherapy period which can trigger accelerated tumor repopulation [28].

Therapeutic strategies targeting CSCS:

Targeting surface markers using monoclonal antibodies directed against surface markers such as CD44 [13] and EpCam, generating significant anti-CSC activity in murine xenografts [29].

Targeting cell signaling pathways whose inappropriate activation stimulates proliferation, limits differentiation and prevents apoptosis playing an important role in the development of cancer [29, 30].

Targeting cellular response mechanisms to DNA damage: Chromosomal DNA is frequently affected by genotoxic events, either by endogenous or exogenous agents, therefore cellular repair to this damage is essential to maintain chromosomal integrity, preventing cells from accumulating mutations and dying.

CSCs have a powerful repairing, superior to that of normal cells, particularly after treatment with radio or chemotherapy [13, 31-33]. Therefore, targeting and blocking this ability can improve the effectiveness of treatments aimed at inducing DNA damage [31].

CONCLUSION

At the end of our work, we were able to elucidate the characteristics of breast cancer stem cells that could explain the aggressive behavior of certain tumors, with an emphasis on CD326, as a biomarker for BCSC, hoping for new therapies in the future that particularly target these cells.

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