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Original Article

Mast cells in invasive ductal breast carcinoma

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Abstract

BACKGROUND: Inflammatory cells in the tumor stroma have gained increasing interests recently. We aimed to study the prognostic impact of the presence of stromal mast cells in invasive breast carcinomas.

METHODS: Tissue sections of 108 cases with invasive breast cancers were prepared and stained with Giemsa. The presence of stromal mast cells were evaluated and its correlation with tumor's grade, tumor size, positivity for estrogen and progesterone receptors (ER and PR, respectively), HER2/neu positivity and lymph node metastasis was analysed.

RESULTS: The median age was 52.3 years (range 28-85 years). Grading was done according to the Nottingham Modification of the Bloom-Richardson system. Fifty-four (50%) women had grade 1, 16 (14.8%) had grade 2 and 38 (35.2%) had grade 3 tumor. The presence of stromal mast cells correlated significantly to low grade tumors ($p = 0.004$) and ER positivity ($p = 0.04$). There was no correlation between the presence of stromal mast cells and the PR positivity, HER2/neu positivity, tumor size and lymph node metastasis ($p > 0.05$).

CONCLUSIONS: Our results indicated that the presence of mast cells in breast cancer is correlated with a much lower grade of this tumor. Also in our study, there was a positive correlation between ER receptor positivity and the presence of mast cells in the stroma of breast cancer.

KEY WORDS: Invasive ductal carcinoma, mast cell, prognosis.

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The stroma surrounding the malignant cells is important for the growth and spread of the malignant tumor. Recently, accumulating evidence suggests that the local inflammatory process, previously believed to be the host response against cancer, might actually contribute to the development of malignancy; and the inflammatory response in the tumors has gained increased attention.[1-4] Recently, the mast cell has emerged as a primary candidate among the infiltrating cell population responsible for mediating tumor promotion.[5-7] Mast cells derived from a specific bone marrow progenitor cell migrate into tissues where they mature depending on the microenvironmental conditions. Mast cells may promote tumor development through many different ways. Mast cells could facilitate tumor angiogenesis through heparin-like molecules and heparin could further permit neovascularization and metastases through its anticlotting effects.[8] But, the issue of heparin role in angiogenesis and tumorigenesis or inhibition of angiogenesis has been a controversial issue in recent literature, and more research is needed to elucidate its exact role in pathogenesis of breast carcinomas.[8-10] Moreover, mast cells secrete histamine nd growth factors, such

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as a vascular endothelial growth factor, platelet derived growth factor, stem cell factor and nerve growth factor. Mast cells are also rich in metalloproteases that contribute to the majority of proteolytic components necessary for tumor invasiveness.[5] On the other hand, mast cells could also be detrimental to tumor growth by secreting several cytokines and proteolytic enzymes participating in inducing apoptosis of the malignant cells, such as IL-4.[11] The dual role of mast cells in inhibiting or promoting tumor growth needs to be further investigated.[12] The first experimental evidence to demonstrate an important correlation between mast cells infiltration and tumor progression was generated in animal models of skin and breast cancer.[13,14] The purpose of this study was to test indirectly the hypothesis that the presence of mast cells in fibrotic regions of breast cancer is correlated with a more favorable prognosis. Our findings are important because they may help to explain the well-known ability of heparin and its derivatives to inhibit the growth of primary and metastatic tumors in various animal models and in humans with cancer.[9,10,15] Although the exact mechanism of this anti-tumor effect mediated by heparin remains uncertain, a number of possible explanations have been proposed, including inhibition of thrombin and fibrin formation, immune system modulation, blockade of tumor cell adhesion to platelets, inhibition of angiogenesis, and functional inhibition of selectin-mediated cell-cell interactions leading to metastasis.[9,15]

Methods

Histologic sections of invasive ductal carcinomas were retrieved from the archive of Department of Pathology, Alzahra Hospital from February 1, 2003 to June 30, 2007. A total of 150 cases were selected randomly. After reviewing the slides that were stained with hematoxylin and eosin, they were reclassified as grade I, II and III according to the Nottingham Modification of the Bloom-Richardson system.[16] Then, tissue sections (5 μm thickness) were prepared from the formalin-fixed, paraffin-embedded tissues and stained with Giemsa staining. Mast cells were counted in high-power field (40 × objective) in each tissue section. We considered a case as mast cell positive only if one or more mast cells were present in stromal areas of specimens in 10 high power fields. Staining for ER and PR was scored according to the method of Reiner et al; i.e., if < 10% of nuclei were stained, they were considered as negative; if ≥ 10% of nuclei were stained, they were considered as positive. Her2 staining was scored according to the Ackerman's Surgical Pathology.[16] Scoring was performed independently by two pathologists and any discrepancies were resolved over a doublehead microscope. Scoring was done without a knowledge of patient history. Slides that failed to illustrate invasive carcinoma and those that didn't have complete immunostainig panel were not scored. Immunostaining results for estrogen receptor (ER), progesterone receptor (PR), HER2/neu, tumor size and lymph node metastasis were collected from the pathology reports. All data were analysed by SPSS (version 15) software. Simple descriptive techniques were used to describe the variables among the participants. The K-S test and Levene's test were applied to verify normal distribution and quality of variances. We used Mann-Whitney U test for comparing the quantitative data in grouping variables. Chi square test was used to find the relationship between qualitative data.

Results

The median age of patients was 52.3 years (range 28-85 years). Thirty-six mast cell positive cases and 72 mast cell negative ones were selected. Thirty-nine cases had positive nodes and 69 cases were node negative. Sixteen (44.4%) of mast cell positive cases had positive lymph nodes in contrast to 31.9% for mast cell negative ones. Distant metastasis was reported in none of our cases. Grading was done according to the Nottingham Modification of the Bloom-Richardson system. Fifty-four women (50%) had grade 1, 16 (14.8%) had grade 2 and 38 (35.2%) had grade 3 tumor (table 1). Mast cells were found mainly in the tumor stroma

adjacent to the neoplastic cells but in some cases mast cells also infiltrated within the islands of tumor cells. The presence of stromal mast cells correlated significantly to low-grade tumors (p = 0.004, table 1) and ER positivity (p = 0.04, table 2). There was no correlation between the presence of stromal mast cells and PR positivity, HER2/neu positivity, tumor size and lymph node metastasis (p > 0.05, tables 3-6).

Table 1. Association between stromal mast cells and histological grade in breast cancer.

Mast Cells / Tumor Grade	With Mast Cell		Without Mast Cell		Total Count	
	Count	Percent	Count	Percent	Count	Percent
Grade I	24	66.6	30	41.6	54	50
Grade II	7	19.5	9	12.6	16	14.8
Grade III	5	13.9	33	45.8	38	35.2
Total	36	100	72	100	108	100

Table 2. Association between stromal mast cells and ER positivity in breast cancer.

Mast Cells / ER	With Mast Cell		Without Mast Cell		Total Count	
	Count	Percent	Count	Percent	Count	Percent
Positive	20	55.6	33	45.8	53	49.1
Negative	16	44.4	39	54.2	55	50.9
Total	36	100	72	100	108	100

Table 3. Association between stromal mast cells and PR positivity in breast cancer.

Mast Cells / PR	With Mast Cell		Without Mast Cell		Total Count	
	Count	Percent	Count	Percent	Count	Percent
Positive	20	55.6	28	38.9	48	44.4
Negative	16	44.4	44	61.1	60	55.6
Total	36	100	72	100	108	100

Table 4. Association between stromal mast cells and lymph nodes positivity in breast cancer.

Mast Cells / Lymph Nodes	With Mast Cell		Without Mast Cell		Total Count	
	Count	Percent	Count	Percent	Count	Percent
Positive	16	44.4	23	31.9	39	36.1
Negative	20	55.6	49	68.1	69	63.9
Total	36	100	72	100	108	100

Table 5. Association between stromal mast cells and HER2/neu positivity in breast cancer.

Mast Cells / HER2/neu	With Mast Cell		Without Mast Cell		Total Count	
	Count	Percent	Count	Percent	Count	Percent
Positive	24	66.7	55	76.4	79	73.1
Negative	12	33.3	17	23.6	29	26.9
Total	36	100	72	100	108	100

Table 6. Association between stromal mast cells and tumor size in breast cancer.

Tumor size	Mean	SD
Mast Cells		
With Mast Cell	4.2	0.4
Without Mast Cell	3.6	0.7
Total	3.7	0.5

Discussion

Identifying new prognostic markers for patients with breast cancers is an important issue since the current treatment guidelines recommend adjuvant treatment for about 90 percent of the patients with node-negative disease, even though only about 30 percent of the patients actually will benefit from the therapy. Thus, it is important to identify new markers for this subgroup of patients who might then not need adjuvant chemotherapy. Few studies of stromal mast cells in invasive breast carcinomas have been done and two studies have indicated that many stromal mast cells are correlated to a favourable prognosis.[17-19] Furthermore, in lymph nodes of women with breast cancers, a higher number of mast cells were found in the non-involved axillary lymph nodes in those women with a better prognosis.[20] In women with axillary lymph node metastasis, more mast cells were found in the non-involved axillary lymph nodes.[21] These findings might indicate a protective effect of mast cells, possibly exerting a cytotoxic effect on the tumor cells. However, the studies are still few and further investigations are needed in order to elucidate the precise role of mast cells in the tumorigenesis. The presence of mast cells was associated to low tumor grade and estrogen receptor positivity. These are factors that are associated with a favorable prognosis in breast cancer. This might, thus be interpreted as that existence of many mast cells is an additive favorable prognostic sign. Mast cells accumulate around tumors and could either promote or inhibit tumor growth depending on the local stromal conditions. The presence of stromal mast cells in other malignant tumors has been of interest, but comprehensive studies are few. In colon cancer, high amounts of mast cells have been associated with lower rates of lymph node metastasis and distant metastasis.[22] In lung cancers, a higher mast cell count has been correlated to tumor progression and also correlated to microvessel density in some studies, but in another study, there was a lack of correlation between mast cells, eosinophils and microvessels.[23] In squamous cell carcinomas of the esophagus[24] and cervix,[25] high numbers of mast cells in the tumors were likewise associated to both microvessel density and tumor progression. Similarly, in malignant melanomas[26] and Hodgkin lymphomas,[27] mast cells have been related to an adverse clinical outcome. The finding of presence of many stromal mast cells close to the microvessel and the association to microvessel density might be explained by contribution of mast cells to neoangiogenesis in these tumors. However, our finding of the correlation of large number of mast cells to favorable prognostic factors in breast cancer indicates that other factors must be taken into consideration. Thus, the presence of stromal mast cells in different tumors and their precise roles in the tumorigenesis need to be further investigated in order to elucidate the different mechanisms behind. In this study, the independent prognostic significance of mast cell infiltrates could not be addressed because the outcome of the patients in this group was not available. New prognostic markers are of more significance in breast cancer because they might influence treatment selection.

Conclusions

Our results indicated that the presence of mast cells in breast cancer is correlated with a much lower grade of this tumor. Also in our study, there was a positive correlation between ER receptor positivity and the presence of mast cells in the stroma of breast cancer. In contrast, as the review of literature depicts, the presence of mast cells is correlated with a poorer prognosis in other tumors such as lymphomas and carcinomas of lung, esophagus, skin and cervix. We can assume that the correlation between the presence of mast cells and a more

favorable prognosis in breast carcinoma perhaps is the result of positive correlation between ER receptor positivity and the presence of mast cells, as it has been shown conclusively that ER receptor positivity is a prognostic factor improving treatment outcome. However, to make this assumption clearer, further research is mandatory.

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