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ORIGINAL ARTICLE

Relationship of mast cell density with lymphangiogenesis and prognostic parameters in breast carcinoma

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Abstract In many cancers, mast cell density (MCD) in the tumor microenvironment is associated with tumor progression and, to a greater extent, angiogenesis. Our study was designed to investigate the correlation between MCD, tumor lymphangiogenesis, and several well-established prognostic parameters in breast cancer. One hundred and four cases of invasive breast carcinoma diagnosed in our clinic between 2007 and 2011 were included. Mast cells and lymphatic vessels were stained with toluidine blue and D2-40, respectively, and their densities were calculated in various areas of tumors and lymph nodes. The variables of MCD and lymphatic vessel density (LVD) were compared using prognostic parameters as well as with each other. As tumor size and volume increased, MCD increased comparably in metastatic lymph nodes; intratumoral and peritumoral LVD also increased. Lymphovascular invasion, lymphatic invasion, perineural invasion, and estrogen receptor positivity were positively related to intratumoral MCD. The relationship between peritumoral MCD and non-tumoral breast tissue MCD was statistically significant. Stage was correlated with MCD in metastatic lymph nodes. Metastatic lymph node MCD and intratumoral MCD were also significantly related. Stage, lymphatic invasion, perineural invasion, lymphovascular invasion, and metastatic lymph node MCD were all correlated with intratumoral and/or peritumoral LVD. As nuclear grade increased, intratumoral LVD became higher. In breast carcinoma, MCD,

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depending on its location, was related to several prognostic parameters. Notably, mast cells may have at least some effect on lymphangiogenesis, which appears to be a predictor of tumor progression.

Introduction

Breast carcinoma is one of the most common cancers in women worldwide and is a serious cause of mortality and morbidity. Despite the accumulation of data on the cellular and genetic properties of breast tumors, their heterogeneous structure and variable clinical behavior are not yet well understood [1]. Recent studies have focused on the modulating effects of cellular and extracellular matrix components that exist in the tumor microenvironment (TME) on tumor progression [2].

There are many innate and adaptive immune cells found in the TME. For example, mast cells (MCs), which have a role in both innate and adaptive immune responses, are the first cells to infiltrate the TME and are known to deliver important regulatory molecules such as proteolytic enzymes, cytokines, and growth factors. Consequently, MCs have a significant impact on tumor biology [3]. Although MCs have a role in modulating the TME in spontaneous or induced cancer models [4], their influence on tumor growth and progression remains unclear. Nevertheless, MCs gather early in the TME and their existence is related to poor prognosis in various aggressive human cancers [5].

Dissolution of the extracellular matrix and basal membrane components plays a significant role in breast cancer invasion and metastasis [6,7]. MCs contribute to this process by the release of neutral proteases; interestingly, the serum level of tryptase was found to be three times higher in breast cancer patients than in healthy individuals [8]. Various studies have shown that the MCs that are the main source of tryptase in tumor tissue, which increases invasion and metastasis, basal membrane disruption, and extracellular matrix dissolution in breast cancer; these cells have also been linked to a poor prognosis [9,10].

Several studies have reported that the microanatomical localization of MCs in the TME has prognostic significance. For example, in prostate cancers, a high density of intratumoral MCs in the TME was related to good prognosis, while a high level of peritumoral MCs was related significantly to poor prognosis and poor survival [11]. In another study, cases of Stage I nonsmall-cell lung cancers with lower densities of peritumoral MCs had a poorer prognosis [12].

Mast cells have a stimulatory role in angiogenesis and lymphangiogenesis by increasing the release of angiogenic factors [vascular endothelial growth factor (VEGF-A, -C, -D] and endostatin under hypoxic conditions [13–16]. In breast carcinoma and many other cancers, MC density (MCD) in peritumoral tissue was found to be closely related to angiogenesis [17]. In addition, lymphatic vessel density (LVD) in tumor tissue is a marker of tumor lymphangiogenesis and can predict the development of lymph node metastasis [18,19]. However, the correlation between MCs and tumor lymphangiogenesis remains to be clarified. In some studies, MC-derived proteases broke down VEGF-C and led to an antilymphangiogenic effect. Some researchers also demonstrated that MCD and LVD were positively correlated, especially in basal-like breast carcinoma [5,18].

The main goal of our study was to investigate the relationship between MCD, which we believed plays a crucial role in tumor progression, and tumor lymphangiogenesis in breast cancer. Additionally, the correlation between the location of MCs (intratumoral, peritumoral, or nonneoplastic breast stroma) and various prognostic parameters were investigated.

Methods

Patients

Cases that were diagnosed and staged as breast carcinoma between 2007 and 2011 at Dr. Lutfi Kirdar Training and Research Hospital Pathology Clinic were included in this study. Patient files and all pathological materials (slides and paraffin blocks) were reviewed and evaluated. The most appropriate paraffin blocks for histochemical and immunohistochemical (IHC) examination were selected. All patients were women who had invasive breast carcinoma. Each case was evaluated for age, tumor size, tumor volume, tumor type, histological grade, nuclear grade, axillary lymph node involvement, lymphovascular invasion (LVI, in hematoxylin-and-eosin-stained slides), lymphatic invasion (LI, in D2-40-stained slides), perineural invasion (PI), estrogen receptor (ER), progesterone receptor (PR), and C-erbB2 staining. Clinicopathological classification and staging were assessed according to the American Joint Committee on Cancer criteria [20–25]. The clinical features of recurrence, metastasis, and death from disease were acquired from patient records.

Patients undergoing neoadjuvant chemotherapy and/or radiotherapy were excluded. Surgical margins were confirmed as negative for all cases included in this study. The patients had no detectable metastasis of the liver, peritoneum, or distant organs at the time of surgery. No other previous or concomitant primary cancer was present. The guidelines of the National Comprehensive Cancer Network were used as a reference when following up and treating the patients [24,25]. Considering the risk of relapse in patients, adjuvant treatments were determined to be chemotherapy and hormone therapy. Patients were followed up from the time of primary surgery until death or January 2016. The median follow-up time for survivors was