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REVIEW

VEGF and EMMPRIN expression correlates with survival of patients with osteosarcoma

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KEYWORDS
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Abstract
Aim: To investigate the clinicopathologic characteristics of Vascular Endothelial Growth Factor (VEGF) and Extracellular Matrix Metalloproteinase Inducer (EMMPRIN) expression in osteosarcoma, and to evaluate the clinical significance of these two markers in the survival of osteosarcoma.
Methods: VEGF and EMMPRIN expression in paraffin-embedded specimens gathered from 65 patients with primary osteosarcoma were detected by the method of immunohistochemistry using antibodies against VEGF and EMMPRIN. The correlation of VEGF and EMMPRIN expression with the clinicopathologic features and with the survival of osteosarcoma was subsequently assessed.
Results: The expression of VEGF and EMMPRIN was detected in 47/65 (72.31%) and 45/65 (69.23%) of patients with osteosarcoma, respectively. Positive expression of VEGF and EMMPRIN was significantly correlated with surgical stage and percentage of dead cells of osteosarcoma. A significant correlation was found between the expression of VEGF and EMMPRIN in osteosarcoma ($r = 0.89$, $p = 0.01$). Additionally, surgical stage, percentage of dead cells, VEGF and EMMPRIN expression showed significant influence on overall survival (OS) and disease-free survival (DFS) in univariate analysis. In multivariate analysis, surgical stage (IIA versus IIB/III) and percentage of dead cells ($\leq$90% versus $>$90%) were significant for DFS and OS. Those patients with VEGF+/EMMPRIN+ co-expression showed significantly shorter OS and DFS compared with VEGF−/EMMPRIN− expression.

Abbreviation: Extracellular Matrix Metalloproteinase Inducer, EMMPRIN; Vascular Endothelial Growth Factor, VEGF; Extracellular matrix, ECM; Matrix metalloproteinases, MMPs.

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Conclusion: According to our study, the overexpression of VEGF or EMMPRIN may be an important feature of osteosarcoma. A combined detection of VEGF/EMMPRIN co-expression may benefit us in prediction of a poor survival of osteosarcoma.
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Contents

Introduction

Osteosarcoma is the most frequent primary malignant bone tumor, accounting for approximately 20% of all primary sarcomas in bone [1]. It occurs predominantly in adolescents and young adults [2]. Although new therapies consisting of aggressive adjuvant chemotherapy and wide tumor excision have led to a significant benefit in terms of patients' survival, it is of great significance to search for sensitive and specific markers that can provide valuable information for the early diagnosis and identification of poorly responsive tumors that may benefit from modified treatment regimen.

Tumor metastasis is a multistep process involving a variety of tumor cell—host cell interactions. Angiogenesis, one such interaction, is the outgrowth of endothelial cells from preexisting capillary vessel and their migration from parental vessels under the stimulation of vascular endothelial growth factor (VEGF) [3], which is a homodimeric protein identified as a mitogen for endothelial cells *in vitro* and an angiogenesis promoting factor *in vivo* [4]. The importance of VEGF in tumor metastasis has been indicated by the correlation between VEGF expression in the primary tumor and the metastatic rates, as well as the poor prognosis for patients with certain malignant tumors, such as gastric carcinoma, colorectal carcinoma, or esophageal carcinoma [5,6]. Proliferating endothelial cells subsequently remodel the extracellular matrix (ECM) via matrix metalloproteinases (MMPs), align into tube-like structures, and eventually form new functional blood vessels. In cancerous cells, overexpression of angiogenic factors, such as VEGF, MMPs, is closely linked to invasion and metastasis of malignancies. The search for MMP-inducing factors in tumor cells leads to the identification of extracellular MMP inducer (EMMPRIN), whose name reflects its EMMPRIN activity [7,8]. Comparing non-tumorous tissues, EMMPRIN is abundant in malignant tumor tissues, facilitating tumor metastasis. The roles of EMMPRIN in tumor invasiveness have been confirmed immunohistochemically in several types of cancer cells, including astrocytomas and melanomas [9]. Moreover, its expression is reported to correlate with the clinical survival of patients with breast carcinoma and other types of cancers [10].

With regard to osteosarcoma, there is a study using a murine model showing the overexpression of VEGF mRNA in a highly metastatic osteosarcoma cell line [11]. The immunohistochemical VEGF expression in the untreated primary site has been reported to be correlated with pulmonary metastasis and microvessel density (MVD) in osteosarcoma [12]. In addition, Wang et al [13] showed poor prognosis in a group of patients with high MVD tumors, whereas Kreuter et al [14] demonstrated that high MVD in the primary tumor was correlated with a good response to chemotherapy and a favorable prognosis in a group of systematically treated osteosarcoma patients. Although several authors have investigated the correlation between VEGF expression in the primary site and the development of metastasis in osteosarcoma [15,16], there is no consensus on the association of VEGF expression in primary site with the prognosis of osteosarcoma patients. Moreover, the expression pattern of EMMPRIN has not been defined in clinical samples of primary osteosarcoma. To elucidate the prognostic role and the correlation of VEGF and EMMPRIN, we examined their immunohistochemical staining patterns in a series of osteosarcoma patients in the present study.

Materials and methods

Patients and tissue samples

The study was approved by the Research Ethics Committee of Ministry of Public Health of China. Informed consent was

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