学 位 論 文 の 要 旨

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学 位 論 文 名　Tumor Angiogenesis in 75 Cases of Pleomorphic Carcinoma of the Lung

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論 文 内 容 の 要 旨

INTRODUCTION

Pleomorphic carcinoma (PC) of the lung is a comparatively rare tumor, which constitutes approximately 0.1-0.4% of all lung cancer cases. PC is usually high grade, aggressive and associated with a poor prognosis. The World Health Organization classification defines pleomorphic carcinoma as "poorly differentiated non-small-cell carcinoma (NSCLC)., namely a squamous cell carcinoma, adenocarcinoma or large cell carcinoma, containing spindle cells and giant cells, and the pleomorphic component should comprise at least 10% of the neoplasm". In the clinic, PC tends to be negative for tumor markers and difficult to diagnose cytologically or histologically using bronchoscopic or computed tomography-guided biopsy. Therefore, the clinical features and behavior of PC remain unclear.

While there have been a few case reports of an association between a bleeding tendency in tumor tissues and abnormalities of angiogenesis, there have been few studies that have made a comprehensive evaluation of angiogenesis in PC. In addition, distant metastasis is frequently observed in cases of PC, and such metastases have tended to expand into regions such as the small intestine, peritoneum, skin, and lymph nodes. Moreover, inflammation and a hypoxic state are also widely recognized to play an important role in tumor angiogenesis through the up-regulation of cyclooxygenase (COX)-2 and hypoxia-inducible factor (HIF)-1α, respectively. COX-2 and HIF-1α are important pro-angiogenic factors that activate the transcription of VEGF.

The aim of the present study was to investigate the clinical features and mechanisms of

angiogenesis in PC, which could lead to the development of new treatments and a more precise diagnosis for patients in the NSCLC.

MATERIALS AND METHODS

We used formalin-fixed, paraffin-embedded blocks from 75 patients with PC who had undergone surgical resection between August 2001 and May 2010 at eight institutes. The staining of VEGF and HIF-1α was assessed semi-quantitatively according to three indices: (i) the percentage of area stained (<10%, 25%, 50%, 75% and 100%), (ii) the intensity of staining (none, 0; weak, +1; moderate, +2; and strong, +3), and (iii) the final score [product of the area and intensity, called the histological (H) score]. In the evaluation of the staining for COX-2, the reactions in vascular endothelial cells, which were present in all specimens, were used as internal "built-in" controls, and cases with tumor cells showing significantly more intense staining than the internal control cells were recorded as being positive. The intensity of staining was graded as follows: weak, +1; moderate, +2; and strong, +3 [called the intensive (I) score]. Vascularity was measured by the average of the microvessel density (MVD). MVD was measured by assessing CD31 immunostaining according to the international consensus report. All immunostained sections were evaluated by four investigators who were blinded to the clinical diagnosis. The protocol was approved by the institutional review board of each institute.

RESULTS AND DISCUSSION

There were 66 males and nine females. The median survival time was 16.5 months. The stage and symptomatical diagnosis were significantly associated with the survival. In the immunohistochemical analyses, vascular endothelial growth factor was expressed in many cases of PC. A high score for angiogenesis was significantly related to a poorer prognosis. The VEGF expression was positive in many cases of PC, so the H scores were high. The mean of all MVDs was 22.8 microvessels/field. We also analyzed the angiogenic score to identify whether the level of angiogenesis in PC may affect the clinical course. According to the angiogenic score, 16 patients were classified in the high-score group, and the other 59 were classified in the low-score group. The MST was significantly different between the groups, with a value of 6.0 months for the high-score group and 21.4 months for the low-score group ($p=0.008$). The surgical and pathological stage (stage IA-IIIA vs. IIIB, IV) and the presence of symptoms at the time of diagnosis (yes vs. no) also significantly differed according to angiogenic score ($p=0.005$ and $p=0.02$). When a Cox proportional hazards model was constructed, which included the stage, symptoms, tumor markers, expression levels of VEGF, COX-2 and HIF-1 α, and the MVD, only the stage and symptoms predicted the overall survival ($p=0.006$ and 0.026, respectively).

CONCLUSION

The results of the current study showed that the stage and presence of symptoms at the time of diagnosis are prognostic factors in PC. Furthermore, tumor angiogenesis provides significant prognostic information about the clinical outcome. These findings suggest that prolonged inflammation and the hypoxic state of tumor cells affect angiogenesis of the tumor, and angiogenesis is related to the progression of PC. Because PCs are rare tumors, the optimal treatment and precise diagnosis remain unclear, with the only data currently available having been obtained from retrospective studies. We believe that our findings will improve the understanding of the clinical characteristics and the behavior of PC of the lung.