学 位 論 文 の 要 旨

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学 位 論 文 名　Stromal Micropapillary Component as a Novel Unfavorable Prognostic Factor of Lung Adenocarcinoma

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論 文 内 容 の 要 旨

INTRODUCTION

Pulmonary adenocarcinomas with a micropapillary component (MPC) having small papillary tufts and lacking a central fibrovascular core are thought to result in poor prognosis. However, the lung MPC consists of tumor cells often floating within alveolar spaces (aerogenous micropapillary component [AMPC]) rather than invading fibrotic stroma observed in micropapillary carcinoma of other organs like breast (stromal invasive micropapillary component [SMPC]). We previously observed cases of lung adenocarcinoma with predominant SMPC that was associated with micropapillary growth of tumors in fibrotic stroma observed in SMPC of other organs. We evaluated the incidence and clinicopathological characteristics of SMPC in lung adenocarcinoma cases.

PATIENTS AND METHODS

We investigated the clinicopathological characteristics and prognostic significance of

SMPC in lung adenocarcinoma cases by reviewing 559 patients who had undergone surgical resection. Furthermore, we examined the SMPC by performing immunohistochemical analysis with 17 antibodies and by genetic analysis with a target for epidermal growth factor receptor (*EGFR*) and *KRAS* mutations.

RESULTS AND DISCUSSION

SMPC-positive (SMPC(+)) tumors were observed in 19 cases (3.4%). The presence of SMPC was significantly associated with tumor size, advanced-stage disease, lymph node metastasis, pleural invasion, lymphatic invasion, and vascular invasion. Patients with SMPC(+) tumors had significantly poorer outcomes than those with SMPC-negative tumors. Multivariate analysis revealed that SMPC was a significant independent prognostic factor of lung adenocarcinoma, especially for disease-free survival of pathological stage I (p-Stage I) patients (p = 0.035). SMPC showed significantly higher expression of E-cadherin and lower expression of CD44 than the corresponding expression levels shown by AMPC and showed lower surfactant apoprotein A and phospho-c-Met expression level than corresponding expression levels shown by tumor cell components without a micropapillary component. Fourteen cases with SMPC(+) tumors showed *EGFR* mutations (74%), and none of them showed *KRAS* mutations.

Prognosis of lung adenocarcinoma with micropapillary MPC has been reported to be worse and have the potential for high malignancy, but no studies have separately evaluated SMPC and AMPC. We showed that SMPC(+) tumors as well as AMPC(+) tumors are associated with several biological factors. The most remarkable finding was observed in multivariate analysis: among the patients in p-stage I, patients with not AMPC but SMPC showed a significantly poorer DFS than those without MPC. When compared with AMPC(+) tumors, SMPC(+) tumors significantly more often showed pleural, lymphatic, and vascular invasion than AMPC(+) tumors.

Moreover, we investigated the immunohistochemical differences between SMPC and AMPC. In the study, we observed high E-cadherin expression and low CD44 expression in SMPC. Phospho-c-Met expression generally decreases in SMPC to a greater extent than in AMPC. Recently, it has been suggested that E-cadherin repression and CD44 expression are associated with the epithelial-mesenchymal transition (EMT) which was thought to lead to tumor invasion. Consistent with these data, EMT may not occur in SMPC despite its existence in the stroma, or invasion of SMPC may occur through a different invasion mechanism from EMT. Our immunohistochemical findings of SMPC showed lower expression of SP-A than that of non-micropapillary component. Many studies have reported that SP-A deletion is correlated with patient survival, and reduced SP-A in MPC may be an excellent indicator for poor prognosis in small-size lung adenocarcinoma. Reduced SP-A may contribute to an unfavorable outcome of SMPC(+) tumors.

Some studies have reported a significant association between the presence of MPC and *EGFR* mutations and effectiveness of EGFR tyrosine kinase inhibitor (EGFR-TKI) for MPC(+) tumors. Because SMPC of lung adenocarcinoma may be associated with a high incidence of *EGFR* mutations, EGFR-TKI may be effective against SMPC(+) tumors. Patients with not only AMPC(+) but SMPC(+) tumors may benefit from EGFR-TKI as postoperative chemotherapy or first-line chemotherapy of relapsed lung adenocarcinoma.

CONCLUSION

SMPC(+) tumors are rare, but recognition of the tumor type is critical because they are associated with a poor prognosis and have different phenotypic and genotypic characteristics from those of AMPC(+) tumors.