学 位 論 文 の 要 旨

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学 位 論 文 名　Cytokeratin 20 (CK20) and Apomucin 1 (MUC1) Expression in Ampullary Carcinoma: Correlation With Tumor Progression and Prognosis

発 表 雑 誌 名
(巻，初頁～終頁等，年)　Diagnostic Pathology
(5:75, 2010)

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論 文 内 容 の 要 旨

INTRODUCTION

Ampullary carcinomas (ACs), although uncommon, have a better prognosis than other periampullary tumors such as pancreatic and bile duct carcinomas. The ampulla of Vater consists of 4 minor anatomic regions: the ampulloduodenum (Ad), the ampullopancreatobiliary common duct (Ac), the ampullopancreatic duct (Ap), and the ampullobiliary duct (Ab). The ampulla is formed by the union of 2 distinct types of mucosa. The Ad is covered by intestinal mucosa, while the other parts of the ampulla of Vater (the Ap, Ab, and Ac) are lined with pancreatobiliary-type ductal mucosa. Therefore, ACs may arise from the intestinal-type mucosa as well as from the pancreatobiliary-type mucosa. Tumor progression and prognosis are affected by the primary AC tumor sites.Determination of the cytokeratin (CK) and apomucin (MUC) immunophenotypes of an AC can facilitate identification of the primary tumor site. We then evaluated the immunohistochemical subtypes of ACs by analyzing the expressions of CK7, CK20, MUC1, MUC2, MUC5AC, and MUC6 in these tumors. Further, we assessed the correlations between the histomorphological findings and the defined immunohistochemical subtypes and evaluated the clinical significance of these immunohistochemical AC subtypes.

MATERIALS AND METHODS

Clinical data were obtained retrospectively from ACs that were surgically resected from 43 patients. All resected specimens had been obtained between 1983 and 2007 and were maintained at the Department of Digestive and General Surgery, Faculty of Medicine, Shimane University. All tumors were classified histologically. The samples were sectioned and stained with hematoxylin and eosin. Subsequently, all tissue samples were stained immunohistochemically with the following antibody panel: monoclonal antibodies to CK7(OV-TL12/30), CK20(Ks20.8), MUC1 (clone Ma695), MUC2 (clone Ccp58), MUC5AC (clone CLH2,), and MUC6 (clone CLH5). Only those samples showing greater than 10% tumor-cell positivity were regarded as positive. Survival curves were calculated by the Kaplan-Meier method and compared with the results of the log-rank test. Agreement between the histological and immunohistochemical classifications was evaluated using the κ-coefficient. A two-tailed Fisher's exact test or χ^2 test was used to compare the immunohistochemical classification and clinicopathological parameters, as appropriate. Probability (p) values of < 0.05 obtained by the two-tailed test were regarded as statistically significant.

RESULTS AND DISCUSSION

The histological classification indicated that CK20 had high sensitivity (100%) for intestinal-type carcinoma and that MUC1 had high sensitivity (94%) for pancreatobiliary-type carcinoma, and both correlations were significant ($p < 0.001$ and $p < 0.001$, respectively). We tried to further classify ACs into 3 subtypes on the basis of the expression of CK20 and MUC1: tumors expressing CK20 and lacking MUC1 were defined as intestinal type (I-type); tumors expressing MUC1 and lacking CK20 were defined as pancreatobiliary type (PB-type); and carcinomas expressing or lacking both CK20 and MUC1 were defined as other type (O-type). Further, the immunohistochemical subtypes defined in our study correlated well with the conventional histological classification (κ-coefficient = 0.518; $p < 0.001$). The immunohistochemical I-type had significantly better pT stage than the immunohistochemical PB-type and O-type tumors (Fisher's exact test, $p = 0.014$ and $p = 0.018$, respectively). The 5-year survival rates for the immunohistochemical I-type, PB-type, and O-type were 55%, 35%,

and 41%, respectively; therefore, there was no significant correlation between survival and immunohistochemical subtypes. Among the patients with immunohistochemical O-type tumors, those with tumors coexpressing MUC5AC/MUC6 had significantly longer cumulative survival than those with tumors that did not show this coexpression ($p = 0.048$). We tried to create a simple AC classification system based on immunohistochemical staining of CKs and MUCs. In the present study, our results indicate that the CK20+/MUC1- pattern fully corresponds to the immunohistochemical I-type and that the CK20-/MUC1+ pattern fully corresponds to the immunohistochemical PB-type. Little is known, however, about the combined expression of CK20 and MUC1 in ACs. The possibility of identifying the primary AC site is increased when the combined expression of CK and MUC, rather the expression of either one of them, is taken into account. In our immunohistochemical classification, the pT stage correlated significantly with the immunohistochemical subtypes. However there were no significant differences in the cumulative survival. This result may be attributable to the lack of differences in the nodal metastasis risks associated with the immunohistochemical I-type and PB-type. Therefore, pancreatoduodenectomy with lymph node dissection should be performed for adequate surgical resection in AC. Gastric differentiation of the immunohistochemical O-type is associated with good prognosis.

CONCLUSION

On the basis of the observed differences in the expression patterns of both CK and MUC, we defined immunohistochemical subtypes. These immunohistochemical subtypes correlated well with the conventional histomorphological classification but did not correlate with prognosis. However, the coexpression of gastric MUC5AC/MUC6 correlates with the prognosis of patients with the immunohistochemical O-type of AC.