Expression and Epigenetic Regulation of E-cadherin in Metastatic Gastrointestinal and Pancreatic Neuroendocrine Tumors and Carcinomas

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Gastrointestinal (GI) and pancreatic neuroendocrine tumors/carcinomas (NET/C) are a heterogeneous group of tumors, behaving differently depending upon their site of origin. Loss of the cell adhesion factor, E-cadherin (E-cadh), characterizes the transition from benign to invasive cancer cells. We undertook this study to investigate the role of epigenetic regulation of E-cadherin in tumor metastasis. NEC resection specimens from different sites in the GI tract and pancreas with available tissue and clinicopathologic information were selected for the study. Sections from the tumors were immunostained with E-CADH antibody and the expression was evaluated independently by tow pathologists. Paraffin-embedded tumor tissue was also microdisected for DNA methylation analysis by pyrosequencing of bisulfate converted DNA. Fifty one cases of (NET/C) included 15 small bowels (SB), 6 appendiceal, 13 pancreatic, 7 rectal, 7 gastric, 1 cecal and 2 liver metastases from pancreatic primary were selected. Lymph node (LN) metastases were present in 16 cases and distant metastases in 4 cases (2 pancreatic and 2 from SB). In the SB, LN metastasis correlated with loss of E-cadh and CDH1 promoter hypermethylation (P = .06), while distant metastasis correlated with cytoplasmic expression of E-cadh (P = .01). In pancreatic NET/C, tumor size correlated with E-cadh expression in the invasive front of the tumor with loss of E-cadh in the tumor center (P = .06) and variable methylation at specific sites of the CDH1 promoter. E-cadh expression in the invasive front of the tumor and LN metastases was associated with CDH1 promoter hypermethylation. Liver metastases from the pancreas showed complete loss of E-cadherin expression and a significant change in CDH1 promoter methylation from the primary tumor. Aggressive behavior of NET/C may be related to the E-cadh pathway through epigenetic regulation. However, it appear to be different from SB versus pancreas, as the metastatic NET/C from SB seem to show a homogenous loss of E-cadh through promoter hypermethylation, while pancreatic NET/C show central loss of E-cadh possibly through a more variable CDH1 promoter methylation. This distinction may explain the difference in response to chemotherapy between SB and pancreatic NET/C. In addition, pancreatic NET/C may metastasize to the LN from their invasive front that expresses E-cadh and to the liver from the center of the tumor that lost E-cadh.

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