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Original contribution

Immunohistochemical distinction between intrahepatic cholangiocarcinoma and pancreatic ductal adenocarcinoma

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Summary Distinction between primary intrahepatic cholangiocarcinoma (ICC) and metastatic pancreatic ductal adenocarcinoma (PDA) on a liver biopsy is essentially impossible histologically but has important clinical implications. In this study, 41 ICCs and 60 PDAs were immunohistochemically evaluated for the expression of S100P, pVHL, IMP3, maspin, MUC5AC, and CK17 proteins. The results showed pVHL expression in 29 (71%) ICCs but in only 3 (5%) PDAs. S100P, MUC5AC, and CK17 were frequently expressed in PDAs, seen in 57 (95%), 40 (67%), and 36 (60%) cases, respectively. In contrast, only 11 (27%), 5 (12%), and 5 (12%) ICC cases expressed these proteins. IMP3 was expressed in 37 (90%) ICC and 54 (90%) PDA cases with equal frequency. All 60 (100%) PDA and 30 (73%) ICC cases showed positive maspin immunoreactivity. A S100P−/pVHL+/MUC5AC−/CK17− staining pattern was essentially indicative of ICC, whereas the S100P+/pVHL−/MUC5AC+/CK17+ and S100P+/pVHL−/MUC5AC−/CK17+ staining patterns were suggestive of PDA. These observations demonstrate that S100P, pVHL, MUC5AC, and CK17 are a useful immunohistochemical panel that may help distinguish primary ICC from metastatic PDA.
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1. Introduction

Distinction between primary intrahepatic cholangiocarcinoma (ICC) and metastatic pancreatic ductal adenocarcinoma (PDA) on a liver biopsy is essentially impossible histologically. It is a frequently asked clinical question, however, because the distinction may have important implications in patient management in terms of surgical options, chemotherapy regimens, and prognosis assessment [1]. Several biomarkers have been studied in this regard, including human pancreatic cancer fusion 2 (HPC2), N-cadherin, and podocalyxin-like protein 1 (PCLP1) [2,3]. However, there has been no single reliable marker proven to be highly sensitive and specific for the distinction between ICC and PDA.

We have recently established the diagnostic value of S100P, the von Hippel-Lindau gene product (pVHL), insulin-like growth factor-II messenger RNA-binding protein-3 (IMP3), and mammary serine protease inhibitor (maspin) for PDA, gallbladder adenocarcinoma, and adenocarcinoma of the extrahepatic bile ducts [4-10]. These studies demonstrated that these biomarkers constitute a useful diagnostic immunohistochemical panel for confirming the diagnosis of adenocarcinoma in difficult cases, which can be helpful in the distinction from normal or reactive epithelium of the pancreas, gallbladder, and extrahepatic bile ducts in surgical, biopsy, and fine-needle aspiration specimens. However, the expression characteristics of

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these biomarkers have not been well studied in ICC. Similarly, immunohistochemical expression of MUC5AC and cytokeratin 17 (CK17) proteins in adenocarcinomas of the pancreas, gallbladder, and bile ducts has been examined in several studies [11-16], but their use in the distinction between ICC and PDA has not been specifically investigated.

In the present study, we specifically compared the expression patterns of S100P, pVHL, IMP3, maspin, MUC5AC, and CK17 proteins between ICC and PDA. Our data demonstrate that an immunohistochemical panel consisting of S100P, pVHL, MUC5AC, and CK17 is useful in distinguishing ICC from PDA.

2. Materials and methods

2.1. Case selection

A total of 41 surgically resected ICCs and 60 surgically resected PDAs retrieved from authors' institutions between 2006 and 2010 were included in this study. Hematoxylin and eosin–stained slides, pathology reports, and pertinent medical records for each case were reviewed to confirm the diagnoses. Cases of hilar or perihilar cholangiocarcinoma were excluded from this study. The ages of the patients with ICC ranged from 36 to 69 years (mean, 58.3 years; median, 58.5 years). The ages of the patients with PDA ranged from 49 to 91 years (mean, 67.7 years; median, 69.0 years). Five ICCs were well differentiated, 22 were moderately differentiated, and 14 were poorly differentiated. Among PDAs, 10 were well differentiated, 35 were moderately differentiated, and 15 were poorly differentiated. All PDAs included in this study were conventional tubular-type ductal carcinomas. Mucinous noncystic carcinomas (colloid carcinomas), signet ring cell carcinomas, and undifferentiated carcinomas were not included. The study was approved by institutional review boards at authors' institutions.

2.2. Immunohistochemistry

Immunohistochemical stains for S100P, pVHL, IMP3, maspin, MUC5AC, and CK17 were performed on 41 ICC cases on routine tissue sections and 60 PDA cases (20 on routine tissue sections and 40 on tissue microarray sections) using previously published protocols on a Dako autostaining system (Dako North America, Inc, Carpinteria, CA) [6,7]. Each PDA case on the tissue microarray section contained two 1.0-mm punches from tumor areas. Detailed information about antibodies and staining conditions is summarized in Table 1. Positive controls included normal kidney tissue for CK17 and pVHL, normal gastric mucosa for MUC5AC, breast tissue (myoepithelial cells) for maspin, placental tissue for S100P, and PDA for IMP3. Negative controls were also included for the stains in which the primary antibodies were replaced with nonhuman-reactive rabbit or mouse serum.

2.3. Evaluation of immunohistochemical stains

Immunohistochemically stained slides were evaluated by 3 investigators (J.L., F.L., H.L.W.). A stain was considered positive if at least 5% of the tumor cells exhibited immunoreactivity. Positive staining was further graded as 1+ (5%-25% of the tumor cells stained), 2+ (26%-50%), 3+ (51%-75%), or 4+ (>75%), as well as weak, intermediate, or strong for staining intensity. Nuclear or nuclear/cytoplasmic staining was considered positive for S100P and maspin; the stain was considered negative if only cytoplasmic staining was detected. Cytoplasmic staining was considered positive for IMP3, MUC5AC, and CK17. Membranous and cytoplasmic staining was considered positive for pVHL.

2.4. Statistical analysis

SPSS 11.5 for Windows software (SPSS Inc, Chicago, IL) was used for statistical analysis. Differences between ICC and PDA were determined by 2-tailed χ^2 test with Yates continuity correction or 2-tailed Fisher exact test. A P value less than .05 was considered statistically significant.

3. Results

3.1. Immunohistochemical findings in ICCs

Cytoplasmic IMP3 immunoreactivity was demonstrated in 37 (90%) of 41 ICC cases, with 25 (68%) cases showing

Table 1 Summary of antibody information and staining conditions

Antibody	Vendor	Clone	Dilution	Incubation time (min)	Antigen retrieval
S100P	BD	16	1:100	30	Proteinase K, pH 7.5, RT, 12 min
pVHL	Santa Cruz	Polyclonal	1:50	30	Proteinase K, pH 7.5, RT, 9 min
IMP3	DAKO	69.1	1:50	40	EDTA, pH 8.0, 100 °C, 15 min
Maspin	BD	G167-70	1:200	40	EDTA, pH 8.0, 100 °C, 15 min
MUC5AC	Vector	CLH2	1:50	60	High pH (9.9), 99 °C, 20 min
CK17	DAKO	E3 (1)	1:80	30	EDTA, pH 8.0, 100 °C, 15 min

NOTE. BD, Becton Dickinson Immunocytometry Systems (BD Biosciences), San Jose, CA; Santa Cruz, Santa Cruz Biotechnology, Inc, Santa Cruz, CA; DAKO, Dako North America, Inc, Carpinteria, CA; Vector, Vector Laboratories, Inc, Burlingame, CA; RT, room temperature; EDTA, ethylenediaminetetraacetic acid.

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