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Intraductal papillary neoplasms of the biliary tract: biliary counterpart of pancreatic IPMNs?

Papillary neoplasms derived from the biliary epithelium are uncommon lesions. They can occur in the intrahepatic and/or extrahepatic biliary tree and occasionally have been found to extend as far as the cystic duct or duodenal papilla. Depending on the localization of the lesion, they are often referred as biliary papillomatosis when diffuse or adenomas/papillomas when localized. Some intraductal papillary neoplasms (IPNs) of the biliary tract are histologically and radiologically similar to intraductal papillary mucinous neoplasms (IPMNs) of the pancreas and present a risk for progression to invasive cholangiocarcinoma. Histologically, both are characterized by intraductal papillary growth of epithelium with fine fibrovascular cores. To date, there are fewer case reports and series of biliary IPNs compared to pancreatic IPMNs. This is probably due to the rarity of biliary IPNs, the lack of histological awareness as to the diagnostic features, and the fact that some infiltrating cholangiocarcinomas may have obliterated the associated intraductal papillary lesion. In addition to the paper in this issue of Lab Invest by **Ishikawa *et al*** (p. 629; see Inside Lab Invest on p. 531), **Abraham *et al*[1]** have performed a molecular and immunohistochemical study of biliary IPNs attempted to address whether biliary IPNs resembled genetically their pancreatic IPMN counterparts, or whether their molecular alterations were more in common with the usual cholangiocarcinomas with which they shared a common tissue origin. The study examined 14 biliary IPNs, including five cases with associated invasive tubular cholangiocarcinoma, for genetic alterations in the *APC/β-catenin* pathway, *K-ras* oncogene, *p53*/chromosome 17p, and *DPC4*/chromosome 18q. Immunohistochemical stains were performed for *β-catenin*, *p53*, and *DPC4*. The authors found that *K-ras* oncogene mutation preceded invasion in biliary IPNs and its frequency (29%) was similar to the reported *K-ras* oncogene mutation in cholangiocarcinomas (approximately 22%), but lower than those of pancreatic IPMNs (approximately 60%). In all, 31% of the cases showed allelic loss of chromosome 18q, but *DPC4* protein expression was intact in all cases examined by immunohistochemistry; which suggested that a non-*DPC4* locus of 18q might be involved. Similar phenomena were seen in cholangiocarcinomas and pancreatic IPMNs. Nuclear accumulation of *β-catenin* protein was observed, but molecular analysis failed to document specific *β-catenin* gene alterations. This suggested the possibility of molecular alterations in other genes involved in regulating cellular *β-catenin,* similar to the reported absence of *β-catenin* mutation in bile duct neoplasms. A low frequency of *β-catenin* gene mutations in pancreatic IPMNs had been reported. There was no significant role of *p53*/chromosome 17p found in the pathogenesis of biliary IPNs in this study. Based on these findings, the authors conclude that biliary IPNs, although histologically resembling pancreatic IPMNs, exhibit certain genetic profiles that are more in common with intrahepatic cholangiocarcinomas with which they share a common tissue origin.

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Reference

1 Abraham SC, Lee JH, Hruban RH, *et al*. Molecular and immunohistochemical analysis of intraductal papillary neoplasms of the biliary tract. Hum Pathol 2003;34:902–910.

Hepatocyte nuclear factor-1 alpha inactivation in familial liver adenomatosis

Liver adenomatosis is a rare condition defined by the presence of multiple adenomas arising in an otherwise normal liver. Although a slight female preponderance is noted, the condition, unlike solitary liver adenoma, is not strongly associated with oral contraceptives or the female gender; an association with maturity-onset diabetes of the young (MODY) has been reported.

The pathogenesis of liver adenomatosis is not known, but two lines of thought prevail. In the first, liver adenomatosis is considered to represent a proliferative response of the liver to as yet unidentified growth factor(s). In the second, it is thought to represent a proliferative response to abnormal vascularity. It is therefore pertinent that a report by **Bacq *et al*[1]** documents the role of inactivation of hepatocyte nuclear factor-1α (HNF-1α) in the development of liver adenomatosis.[1] HNF-1α is a homeodomain containing transcription factor expressed in the liver and kidney that acts exclusively on genes expressed in the liver. Biallelic inactivation of HNF-1α, mostly by somatic mutations, has been identified in hepatocellular adenomas and adenomatosis. Heterozygous germline mutations of HNF-1α result in maturity-onset diabetes of the young type 3 (MODY3), a type of nonketotic diabetes with onset in young adults under 25 years of age. The paper by Bacq *et al* documents an association between heterozygous

germline mutation of HNF-1α, liver adenomatosis and MODY3 in two families. There seems to be an incomplete penetrance of both the diabetic and adenomatosis phenotype in these patients. Germline mutations resulted in premature stop codons thus inactivating one allele of HNF-1α; in tissue from the adenomas, the second allele was inactivated by a gene deletion. This behavior suggests that HNF-1α behaves like a tumor suppressor gene. This observation is the first definitive molecular insight into pathogenesis of liver cell adenomas. The exact mechanisms linking abnormal glucose metabolism and liver adenomatosis are uncertain. This relationship may be entirely fortuitous or constitute an interplay of genetic and hormonal factors. Regardless, the identification of a patient with liver adenomatosis or MODY3 justifies screening other family members for diabetes, liver lesions and HNF-1α mutations.

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Reference

1 Bacq Y, Jacquemin E, Balabaud C, *et al*. Familial liver adenomatosis associated with hepatocyte nuclear factor1 alpha inactivation. Gastroenterology 2003;125:1470–1475.