Histopathologic features and microsatellite instability of cancers of the papilla of Vater and their precursor lesions.

Abstract:

The prevalence and development of microsatellite instability (MSI) and underlying mismatch repair (MMR) deficiency in the carcinogenesis of adenocarcinomas of the papilla of Vater and their precursor lesions are not well established. We analyzed 120 ampullary adenomas (31 pure adenomas and 89 carcinoma-associated adenomas) and 170 pure adenocarcinomas for MSI, immunohistochemical expression of MMR proteins and specific histopathologic features. The most common histologic subtype was intestinal (46.5%), followed by pancreatobiliary (23.5%), poorly differentiated adenocarcinomas (12.9%), intestinal-mucinous (8.2%), and invasive papillary carcinomas (5.3%). Eight of 89 adenomas (9%) and 15/144 carcinomas (10%) showed high microsatellite instability (MSI-H), 10/89 adenomas (11%) and 5/144 carcinomas (4%) showed low microsatellite instability (MSI-L), and 71/89 adenomas (80%) and 124/144 carcinomas (86%) were microsatellite stable (MSS). MSI analysis from carcinomas contiguous with an adenomatous component (n=54) exhibited concordant results in 6/8 (75%) MSI-H and 42/46 (91.3%)
MSS tumors. Of 14 carcinomas with MSI-H, 7 showed loss of MLH1 and 5/6 (83%) MLH1 promoter methylation, and 2 carcinomas showed simultaneous loss of MSH2 and MSH6. Two carcinomas and 3 adenomas with MSI-H revealed exclusive loss of MSH6. MSI-H cancers were significantly associated with intestinal mucinous subtype (P<0.001), high tumor grade (P=0.003), expansive growth pattern (P=0.044), and marked lymphoid host response (P=0.004). Patients with MSI-H carcinoma had a significantly longer overall survival (P=0.0082) than those with MSI-L or MSS tumors. Our findings indicate that the MSI-phenotype is an early event, which develops at the stage of adenoma and is reliably detectable in the precursor lesion. The MMR deficient molecular pathway of carcinogenesis is associated with a histopathologic phenotype in ampullary cancer, similar to the one that has been well described in colon cancer.