Malignant Tumours of the Biliary Tract.

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Neoplasia involving the biliary tract is relatively uncommon although is of concern to the general pathologist in two important scenarios. The first is in the assessment of incidental benign lesions noted at the time of abdominal surgery, frequently being performed for gastrointestinal malignancy and which frequently takes the form of a frozen section diagnosis. Secondly when the pathologist is faced with a liver biopsy performed for presumed malignancy, frequently with the accompanying clinical history of ? metastasis; sometimes ? abscess ? lymphoma ? primary and ? other... With increasing frequency, several of these lesions actually are intrahepatic cholangiocarcinoma with obvious implications for treatment options and management.

Cholangiocarcinoma is a relatively rare tumour and which shows striking geographical variation in its incidence. The classification of these lesions is slightly complex but predominantly related to where they arise within the anatomical biliary tree. Traditionally they are divided into intrahepatic and extrahepatic lesions, (distal common bile duct, gallbladder or in the proximal bile duct). Latter tumours include those at the hilum and these can be further subclassified, important for decision-making in surgical intervention. Whatever the site, these lesions are often further classified into mass forming, periductal-infiltrating (sclerosing) or intraductal (papillary).

There are well established risk factors for cholangiocarcinoma, the majority of which result in chronic inflammation and bile stasis, with or without superadded infection, somewhere within the biliary tree. The highest incidence worldwide is in Thailand and associated with liver fluke infestation; the major risk factor in the UK is pre-existing primary sclerosing cholangitis. Other, more rare entities include congenital abnormalities of the biliary tract, gallstones, hepatolithiasis, cirrhosis, biliary papillomatosis and toxins.

The clinical presentation may either be due to obstruction within the biliary tract, particularly if extrahepatic or with general systemic features of malignancy and often at an advanced stage, particularly of intrahepatic. Rarely is the lesion noted when investigating abnormal liver function tests; these frequently have an obstructive pattern with raised alkaline phosphatase, gamma glutamyl transpeptidase and bilirubin. Tumour markers are not highly specific nor sensitive although CA 19-9 is elevated in the majority of patients with cholangiocarcinoma and to a lesser extent CA 125 and CEA.

The vast majority of cholangiocarcinomas at all sites are adenocarcinoma; the extrahepatic lesions may have a greater range. The WHO classification lists all.
Cholangiocarcinoma consists predominantly of cuboidal to columnar cells, frequently with well formed glands, within a prominent fibrous stroma; mucin can be demonstrated. There is strong expression on immunohistochemical staining for cytokeratin 7, cytokeratin 19 with also positivity for CA 19-9, frequently CEA 125 and CEA. They are normally negative for HepPar1.

The incidence of intrahepatic cholangiocarcinoma has increased in the last few decades within the UK. Such rises, and concomitant increase in mortality, has been seen in many other industrialised countries, including the USA, France, Australia and Japan. The reason has not been established although the rapidity suggests some environmental factor.
The molecular changes resulting in neoplasia appear related to the constant pro-inflammatory environment and occur in a typical multistep process. Inflammatory mediators, in particular interleukin IL-6 appears pivotal in promoting autologous proliferation (also K-ras, EGFR, c-erb-2,COX-2), with escape from senescence (p 53, p 21, p 16 mutations, teleromase expression) and evasion of apoptosis (Bcl-2, Bcl-XL, Mcl-1, NO). Further alterations lead to the potential for invasion and metastasis, including angiogenesis (VEGF, E-cadherin, alpha- and beta-catenin, MMP and Aspartyl beta-hydroxylase).

One uncommon variant of cholangiocarcinoma has mixed features with hepatocellular carcinoma. There is a growing interest in these tumours as there is some evidence that they are derived from progenitor, or stem cells, within the liver and may give insight into the pathobiology of these cells.

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