Adenocarcinoma of the bile ducts and gallbladder.

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Cholangiocarcinoma (CCA) is a rare adenocarcinoma arising from any part of the biliary tree. On the basis of its anatomic location and according to World Health Organization Classification, CCA can be classified as intrahepatic (IH, ~10-25%) and extrahepatic (EH). These latter are further subdivided into hilar (H, ~50-60%), middle and distal EH carcinoma (~20-30%), and gallbladder carcinoma (GB, ~10-25%). IH-CCA is the second most common primary hepatic malignancy after hepatocellular carcinoma. Both its incidence and mortality around the world are continuously increasing, whereas those of GB and EH-CCA are remaining constant or decreasing. H-CCA (Klatskin tumor), the most frequent, involves the hepatic duct confluence and intrahepatic large bile ducts. Intrahepatic and extrahepatic CCAs are differentiated, as they differ in etiopathogenesis, symptoms, management and prognosis.
CCA is associated with conditions that cause chronic biliary tract inflammation, such as primary sclerosing cholangitis, liver fluke infestation (clonorchis sinensis, opisthorchis viverrini), chronic viral hepatitis, pancreaticobiliary maljunction, cystic disease... Because of various distributions of local risk factors, there is a significant geographic variation in its incidence. CCAs derived from a different level of biliary ducts are related to different risk factors. IH-CCA frequently occurs in a non-cirrhotic liver, although there are increasing reports in cirrhotic liver.
Cholangiocarcinogenesis develops through a multistep histopathologic sequence from hyperplasia, dysplasia (superimposed metaplasia is not infrequent) to cancer.

A - Premalignant precursor lesions

Two premalignant or non-invasive neoplastic lesions are proposed in the tumorigenesis of CCA : 1) biliary intra-epithelial neoplasia (BilIN) or dysplasia, a flat-type, and 2) intraductal papillary neoplasm of the bile ducts (IPN), a papillary-type. They are probably analogous to pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasm. Both occur preferentially in chronic biliary diseases, particularly arising in hepatolithiasis.
1. 'Biliary intraepithelial neoplasia (BilIN) is more common. This is a flat or micropapillary microscopic epithelial lesion, not grossly identifiable. It is usually diagnosed in large-sized bile ducts or GB. BilIN is classified as low or high grade (WHO) or graded as mild, moderate or severe according to a three-grade consensus classification system proposed in 2005. It is characterized by cuboidal or columnar cells showing variable degrees of nuclear pseudostratification, cellular/nuclear atypia, loss of polarity and mitotic figures. When present, discrimination is important, because mitoses in BilIN suggest the diagnosis of higher grade lesions, mostly BilIN-3. The lesions usually begin on the surface and subsequently extend laterally and downward into the Rokitansky sinuses or peri biliary glands.
Mimickers of BilIN:
Reactive atypia may mimick BilIN1. The presence of significant inflammation with intraepithelial neutrophilic infiltration could raise this possibility. Mitoses can be observed. Cellular changes are gradual in contrast to the abrupt transition seen in BilIN.
Carcinoma in situ extending downward into Rokitansky sinuses or peri biliary glands may mimic infiltrating carcinoma.

2. Intraductal papillary neoplasm of the bile ducts (IPN) are uncommon lesions that may be solitary or may spread extensively along the biliary tree and even extend into the GB, small IH bile ducts (BD) and main pancreatic duct. They are visible grossly and by imaging. Dilated BD are filled with papillary or villous excrescences with mucin hypersecretion. Intra ductal spread and peribiliary glandular involvement, or progression to invasive cholangiocarcinoma will be detected by serial cross sections from the entire area of the resected biliary tree.

IPN consists of complex papillary and gland structures, lined by cells with a pancreatobiliary, intestinal, gastric, or oncocytic phenotype based on morphology of the cells and expression of MUC1, MUC2, and MUC5 gene proteins in the mucin family. They are classified as adenoma, borderline tumor and in situ carcinoma. They can be considered as a counterpart of intraductal papillary mucinous neoplasm of the pancreas, particularly the main duct type.
Acute repeated episodes of cholangitis or obstructive jaundice are frequent clinical manifestations. Mucobilia is specific for their diagnosis.

3) Adenomas, are benign polypoid neoplasms grossly visible. They are more common in the GB than in the EH-BD. Thet are divided into 3 types: tubular, papillary and tubulo-papillary type.

B - Early bile duct carcinoma

Early BD cancer is defined as a carcinoma whose invasion is confined within the fibromuscular layer of the extrahepatic bile duct or intrahepatic large BD, without distant metastasis, irrespective of lymph node involvement. Peripheral cholangiocarcinoma is excluded from this concept as intrahepatic small bile ducts lack a fibromuscular layer in the wall. Their incidence in the literature (mainly originating from Japan and South Korea) is approximately 3%-10% of resected bile duct cancers.
Gross appearance varies from no or minimal mucosal changes to an intraductal papillary mass.
Histology: papillary adenocarcinoma is more common (31%-90%) than tubular adenocarcinoma.
Early BD adenocarcinoma has a markedly better surgical outcomes (5-year survival rate of 80%) than advanced bile duct cancer patients.

C - Overt bile duct carcinoma, general features

1. The Liver Cancer Study Group of Japan has recently proposed that BD cancers could be classified as one of three types based on **gross morphology**: (1) The mass forming type is reported to be the most common gross type of P-CCA. It presents as a whitish rounded hard tumor, arising in a non-cirrhotic liver or with underlying liver cirrhosis. It is associated with intrahepatic metastases, similar to hepatocellular carcinoma. The extremely unfavorable prognosis of this type even after surgical resection, is mainly due to the advanced clinical stage. (2) The periductal-infiltrating type is reported to be the most common gross type of extrahepatic bile duct cancer. It extends mainly longitudinally along the bile duct, often resulting in dilatation of the peripheral bile duct. (3) intraductal-growing type is the least common among IH CCA but the most common gross type of early bile duct cancer. It is distinguished from other types because a favorable prognosis can be expected after surgical resection. It presents as a papillary, bulky or granular tumor that grows into the bile duct. This type has the highest resectability rates. This gross classification is correlated with natural history, imaging and prognosis of CCA.

2. Histopathology: Most peripheral type CCA (P-CCA) arising from small biliary epithelium, have histologic features of small-sized glands in a fibrotic background, closely packed, somewhat distorted small ducts, and cordlike structures. Cell type is bland cuboidal as a rule. The nucleus is uniform central with inconspicuous nucleoli. The cytoplasm is usually clear but sometimes granular. Bile production is never found. Stains for mucin production are usually positive and provide a useful test for distinguishing CCA from pseudoglandular hepatocellular carcinoma (HCC), which by definition is mucin(-).The desmoplastic reaction is variable and characteristic, giving much more scirrhous features that does HCC. CCA and metastasis may look very similar pathologically, so the primary diagnostic challenge facing the surgical pathologist is to distinguish them from metastatic adenocarcinoma (especially pancreatic carcinoma).
EH type CCA (EH-CCA) arising from large IH-BD or EH-BD, have histologic features of a papillary epithelial component or a large tubular component composed of tall columnar cells.
Most GB carcinoma are well to moderately differenciated adenocarcinoma. Usually they exhibit different growth patterns and varying degrees of differentiation. Moreover, they are cytologically

heterogeneous, contain a mixture of cell types, with a biliary or intestinal phenotype, and in a small proportion of cases, gastric foveolar type.

3. Immunophenotype : normal biliary cells are cytokeratins (CK) CK7(+) CK8(+) CK18(+) CK19(+). Normal hepatocytes are CK7(-) CK8(+) CK18(+) CK19(-) HepPar1(+). Colonic cells are CK7(-) CK20(+). CCA is CK7(+) CK8(+) partially CK20(+) (more frequent in the hilar type) CK19(+) ACEp(+) and HepPar1(-).The combined immunostaining of CK7 and 20 helps to differentiate cholangiocarcinoma from metastatic adenocarcinomas from colorectal and gastric regions. But the CK7(+) CK20(-) immunoprofile is nonspecific and can be observed in other pancreatobiliary and breast malignancies.

4. Variants: Combined hepatocellular-cholangiocarcinoma is a rare form of primary liver cancer (< 5%) showing features of both hepatocellular and biliary epithelial differentiation. 2 histologic types are encountered: "collision tumors," defined as occurrence of both CCA & HCC (biphenotypic differentiation) and « transitional tumors," in which there are areas of intermediate differentiation and an identifiable transition between HCC and CCA. Most combined CCA - HCC are associated with hepatitis C/ B viral-related cirrhosis. They arise from progenitor cells that retained their potential to differentiate into the hepatocytic and biliary lineages.
Occasionnal tumors demonstrate squamous différenciation**.**
CCA with sarcomatoid features is a rare but aggressive malignancy

D - Overt CCA: radiologic-pathologic correlation and spread according to anatomic location

1. P-CCA :

Most are infiltrating nodular lesion. There is rarely peripheral necrosis. Histologically they present as well-differentiated adenocarcinoma (ADK) with an abundant fibrous stroma. They are locally aggressive tumor, with secondary growth to the BD (sometimes distant from the main tumor), Glisson's capsule, bed of the GB, perineural/ vascular invasion and satellite nodules. P-CCA tends to spread to the hilar and peri pancreatic lymph nodes earlier than do HCC (nodes meta occur in about 40% of P CCA vs 10% for CHC). Distant blood stream spread is rare compared with that of HCC.
The typical CT features of a mass-forming P-CCA is usually a rim enhancement at the periphery, and at delayed phase scanning, a higher attenuation than does the surrounding liver, a finding that is related to abundant fibrous stroma. Capsular retraction, satellite nodules, and peripheral intrahepatic duct dilatation are also typical pattern .
Prognosis is dismal, with a median survival time measured in months and essentially no long term survivors, which has not changed significantly over the past 30 years. Such poor survival is mainly due to late diagnosis and that few patients are candidates for radical surgery which represents the only curative option. Prognosis is dependant on: tumor size > 2 cm, satellite nodules, lymph node metastasis, resectability rate, negative surgical margins.

2. Hilar and EH-CCA

Most are of a periductal infiltrating (PI) type, characterized by a linear/ longitudinal growth along the dilated or narrowed bile duct. On gross examination, the diffuse thickening of the wall may be obscured by dense fibrosis. Histologically, ADK is well-differentiated with a fibrous or oedematous stroma. Tubular glands infiltrate between peribiliary glands. Peri neural infiltration is more frequent than in P-CCA. The most distinguishable imaging pattern of PI type is diffuse ductal dilatation and a focal stricture, with a non-demonstrable mass, or a periductal thickening and increased enhancement due to tumor infiltration.

Some present an extensive intra ductal papillary growth, showing a cauliflower-like appearance and intraluminal spread. Papillary (and nodular types) have grossly evident tumorous lesions. On imaging, intraductal CCA may manifest with various patterns: diffuse or localized variable ductal dilatation, sometimes with an intraductal papillary or polypoid mass, or castlike lesions within a mildly dilated duct, or a focal stricture-like lesion.

3. Longitudinal spread

Hilar and EH-CCAs often grow longitudinally along the bile duct rather than in a radial direction and present a characteristic, either mucosal (superficial spread) or submucosal (periductal) longitudinal extension at the proximal border. Mucosal extension is observed more often in ID papillary or nodular tumors. Submucosal extension is characteristic of infiltrating tumors (either peri ductal or nodular). Perineural and lymphatic invasion proved to be common routes of submucosal extension. Submucosal extension is less than 10 mm in most of patients but mucosal extension of more than 20 mm is reported. So, a 10-mm margin is required for eradication of invasive EH-CCA. Additional removal of any non-invasive component requires a 20-mm margin. Such extension is not apparent on imaging or operatively. Frozen sections is used to ensure a negative surgical margin.

4. Gallbladder carcinoma

Gallbladder carcinoma may arise in a porcelaneous gallbladder, a premalignant condition characterized by diffuse calcification of the wall. Grossly, it is divided into a polypoid exophytic mass, a diffuse wall thickening or an infiltrating mass. Some, may be difficult to distinguish from chronic cholecystitis. Gallbladder carcinoma has a propensity to spread to liver parenchyma, hepatoduodenal ligament and peritoneum by means of direct extension, lymphatic/ venous spread and peri neural dissemination. Distant metastatic nodules, with or without direct invasion, may be observed. Staging laparoscopy may identify occult dissemination that can be missed on preoperative imaging and avoid unnecessary explorations.
US , CT or MRI reveal a mass replacing the gallblader, the most common pattern of GB cancer. A diffuse or focal thickening of the wall can be similar in appearance to chronic cholecystitis.

References

(1) Chung YE, Kim MJ, Park YN, Choi JY, Pyo JY, Kim YC, Cho HJ, Kim KA, Choi SY. Varying appearances of cholangiocarcinoma: radiologic-pathologic correlation. Radiographics 2009; 29(3):683-700.

(2) Malouf G, Dreyer C, Guedj N, Paradis V, Degos F, Belghiti J, Le Tourneau C, Faivre S, Raymond E. [Prognosis factors of cholangiocarcinoma: contribution of recent molecular biology tools]. Bull Cancer 2009; 96(4):405-415.

(3) Nakanuma Y, Zen Y, Harada K, Ikeda H, Sato Y, Uehara T, Sasaki M. Tumorigenesis and phenotypic characteristics of mucin-producing bile duct tumors: an immunohistochemical approach. J Hepatobiliary Pancreat Surg 2009.

(4) Nakanishi Y, Zen Y, Kawakami H, Kubota K, Itoh T, Hirano S, Tanaka E, Nakanuma Y, Kondo S. Extrahepatic bile duct carcinoma with extensive intraepithelial spread: a clinicopathological study of 21 cases. Mod Pathol 2008; 21(7):807-816.

(5) Nakanuma Y, Sasaki M, Ikeda H, Sato Y, Zen Y, Kosaka K, Harada K. Pathology of peripheral intrahepatic cholangiocarcinoma with reference to tumorigenesis. Hepatol Res 2008; 38(4):325-334.

(6) Aishima S, Kuroda Y, Nishihara Y, Iguchi T, Taguchi K, Taketomi A, Maehara Y, Tsuneyoshi M. Proposal of progression model for intrahepatic cholangiocarcinoma: clinicopathologic differences between hilar type and peripheral type. Am J Surg Pathol 2007; 31(7):1059-1067.

(7) Cha JM, Kim MH, Jang SJ. Early bile duct cancer. World J Gastroenterol 2007; 13(25):3409-3416.

(8) Zen Y, Adsay NV, Bardadin K, Colombari R, Ferrell L, Haga H, Hong SM, Hytiroglou P, Kloppel G, Lauwers GY, van Leeuwen DJ, Notohara K, Oshima K, Quaglia A, Sasaki M, Sessa F, Suriawinata A, Tsui W, Atomi Y, Nakanuma Y. Biliary intraepithelial neoplasia: an international interobserver agreement study and proposal for diagnostic criteria. Mod Pathol 2007; 20(6):701-709.

(9) Cha JM, Kim MH, Lee SK, Seo DW, Lee SS, Lee JH, Lee SG, Jang SJ. Clinicopathological review of 61 patients with early bile duct cancer. Clin Oncol (R Coll Radiol) 2006; 18(9):669-677.

(10) Goere D, Wagholikar GD, Pessaux P, Carrere N, Sibert A, Vilgrain V, Sauvanet A, Belghiti J. Utility of staging laparoscopy in subsets of biliary cancers : laparoscopy is a powerful diagnostic tool in patients with intrahepatic and gallbladder carcinoma. Surg Endosc 2006; 20(5):721-725.

(11) Nakanuma Y, Harada K, Ishikawa A, Zen Y, Sasaki M. Anatomic and molecular pathology of intrahepatic cholangiocarcinoma. J Hepatobiliary Pancreat Surg 2003; 10(4):265-281.

(12) Yamasaki S. Intrahepatic cholangiocarcinoma: macroscopic type and stage classification. J Hepatobiliary Pancreat Surg 2003; 10(4):288-291.

(13) Nakanuma Y, Sasaki M, Ishikawa A, Tsui W, Chen TC, Huang SF. Biliary papillary neoplasm of the liver. Histol Histopathol 2002; 17(3):851-861.

(14) Sakamoto E, Nimura Y, Hayakawa N, Kamiya J, Kondo S, Nagino M, Kanai M, Miyachi M, Uesaka K. The pattern of infiltration at the proximal border of hilar bile duct carcinoma: a histologic analysis of 62 resected cases. Ann Surg 1998; 227(3):405-411.

(15) Nakeeb A, Pitt HA, Sohn TA, Coleman J, Abrams RA, Piantadosi S, Hruban RH, Lillemoe KD, Yeo CJ, Cameron JL. Cholangiocarcinoma. A spectrum of intrahepatic, perihilar, and distal tumors. Ann Surg 1996; 224(4):463-473.

(16) Nakajima T, Kondo Y, Miyazaki M, Okui K. A histopathologic study of 102 cases of intrahepatic cholangiocarcinoma: Histologic classification and modes of spreading. Human Pathology 1988; 19(10):1228-1234.