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Review Article

The Omphalic Canker-Intrahepatic Cholangiocarcinoma

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Abstract

Intrahepatic cholangiocarcinoma emerges as a malignant, intrahepatic, epithelial neoplasm delineating biliary differentiation. As categorized by World Health Organization (WHO) in 2019, neoplasm may incriminate peripheral hepatic parenchyma or arise proximal to left hepatic duct and right hepatic duct. Additionally designated as peripheral cholangiocarcinoma or intrahepatic bile duct carcinoma, the non encapsulated, firm, white or tan intrahepatic glandular malignancy demonstrates variable cellular differentiation with cellular or nuclear atypia. Neoplasm appears to infiltrate circumscribing dense, fibrous stroma.

Keywords: World Health Organization (WHO); Peripheral Hepatic Parenchyma

Introduction

Intrahepatic cholangiocarcinoma is classified as small duct subtype and large duct subtype which can be distinguished upon cogent morphological and molecular assessment.

Macroscopically, a distinctive tumefaction, periductal infiltrating lesion, intra-ductal neoplasm or mixed growth pattern may be encountered. However, aforesaid subcategories lack prognostic significance.

Intrahepatic cholangiocarcinoma is posited to arise from stem cells inhabiting canals of Hering or stem cells confined within peribiliary glands [1,2].

Large duct subtype may arise secondary to conditions such as primary sclerosing cholangitis or infestation with liver flukes. Frequently, the neoplasm manifests as a hilar tumefaction or obstructive cholestasis.

Small duct subtype may occur due to viral hepatitis or non biliary cirrhosis and represents as an enlarged tumefaction confined to peripheral hepatic parenchyma.

Intrahepatic cholangiocarcinoma configures an estimated 15% of primary hepatic malignancies and ~10% of bile duct carcinomas. Majority of incriminated subjects appear between 55 years to 75 years. A male predilection is observed [1,2].

Intrahepatic cholangiocarcinoma is posited to arise due to chronic inflammation of intrahepatic bile ducts with perpetual signalling on account of activation of IL6-STAT3 pathway.

Neoplasm depicts genomic mutations within IDH, EPHA2 or BAP1 genes. Besides, genomic fusion within FGFR2 may ensue along with TP53 and SMAD4 genetic mutations.

Intrahepatic cholangiocarcinoma demonstrates genomic mutations within KRAS, BRAF, EGFR, IDH1 / IDH2 or MET genes. Besides, activation of mTOR, overexpression of cyclin D1, overexpression of p21 and inactivating mutations within DPC4/ SMAD4 or TP53 are encountered [1,2].

Tumefaction demonstrates gains within chromosome 1q, 5p, 7p, 8q, 17q and 20q and losses within chromosomes 1p, 4q, 8p, 9p, 17p and 18q. Cholangiocarcinoma associated with infestation by liver flukes demonstrates CpG island hyper-methylation.

Chronic inflammation of biliary epithelium and bile stasis are common contributors to emergence of intrahepatic cholangiocarcinoma.

Small duct subtype may ensue due to non biliary cirrhosis, alcoholic steatohepatitis or non alcoholic steatohepatitis (NASH) and hepatitis B or hepatitis C [2,3].

Large duct subtype may emerge as a consequence to primary sclerosing cholangitis, infestation with hepatobiliary parasites as Opisthorchis viverrini, Clonorchis sinensis, hepatolithiasis, Caroli's disease, type I and type IV choledochal cysts, multiple bile duct hamartomas as encountered within von_Meyenburg_complexes or administration of thorotrast [2,3].

Preliminary lesions appear asymptomatic. Delayed disease stage is accompanied by nonspecific clinical symptoms as abdominal pain, malaise, pyrexia, night sweats, loss of weight or cachexia.

In contrast to extrahepatic cholangiocarcinoma, hyperbilirubinemia or biliary obstruction is infrequently discerned in intrahepatic cholangiocarcinoma [2,3].

Intrahepatic cholangiocarcinoma manifests as an enlarged, nodular, non encapsulated, well demarcated, firm, white, tan or grey intrahepatic tumefaction. Right lobe of liver is frequently incriminated. Satellite tumour nodules or focal calcification may be discerned. Majority of neoplasms exhibit tumour nodules intermingled with non cirrhotic hepatic parenchyma [2,3].

Grossly, neoplasm is categorized as

- Mass forming with occurrence of solid tumefaction within hepatic parenchyma
- Periductal infiltrating wherein tumour infiltration occurs within portal tracts along with configuration of bile duct strictures
- Intra-ductal growth with discernible papillary or polypoid tumefaction permeating a distended bile duct.

Frozen section is optimal for determining status of surgical margins. Invasive foci of cholangiocarcinoma configure infiltrating glandular articulations engendering direct stromal invasion, vascular invasion or perineural invasion [2,3].

Upon cytological examination, isolated clusters and sheets of cuboidal or columnar epithelial cells are encountered. Tumour cells demonstrate variable nuclear enlargement or cellular and nuclear pleomorphism.

Upon cytological examination of cell block, significant glandular differentiation is observed.

Upon fine needle aspiration, an estimated > 10 proliferating ductules aids in segregating cholangiocarcinoma from metastatic adenocarcinoma [2,3].

Upon microscopy, intrahepatic cholangiocarcinoma is comprised of well formed or cribriform glandular articulations infiltrating an abundant, circumscribing fibrous stroma. Neoplastic glands are layered with cells delineating variable cellular and nuclear atypia and pleomorphism.

Well differentiated adenocarcinoma exhibits mild cellular and nuclear atypia, intracytoplasmic lumens and intraluminal cellular debris. Focal atypia with significant pleomorphism may be discerned.

Commonly, tumefaction infiltrates between cords of hepatic parenchyma situated within periphery of tumour. Neoplasm may be multi-centric. Frequently, perineural invasion may ensue.

Intrahepatic cholangiocarcinoma exhibits cogent histologic variants as mucinous, signet ring cell, clear cell, lymphoepithelioma-like, thyroid follicular-like, adenosquamous or sarcomatoid [2,3].

Small duct subtype of intrahepatic cholangiocarcinoma may configure a tumour mass confined within peripheral hepatic parenchyma. Neoplastic glands are layered with cuboidal cells configuring miniature tubular articulations or anastomosing glandular structures. Variable foci of lymphatic, vascular or perineural tumour invasion are encountered. Tumour cells appear immune reactive to CD56, N-cadherin or c-reactive protein (CRP). Neoplasm demonstrates cogent subtype as cholangiolocarcinoma or intrahepatic cholangiocarcinoma with ductal plate malformation-like pattern [2,3].

Large duct subtype of intrahepatic cholangiocarcinoma appears proximal to hepatic hilum and manifests as an infiltrative, periductal lesion or distinctive tumour nodule. Neoplastic glands appear enlarged and are layered with mucin secreting, tall columnar epithelium with open glandular lumens.

Biliary intraepithelial neoplasia, intra-ductal papillary neoplasm of bile duct (IPNB) or intra-ductal tubular papillary neoplasm (ITPN) are precursors to the neoplasm.

Foci of lymphoid, vascular or perineural invasion may be observed. Tumour cells appear immune reactive to MUC5AC, MUC6, S100P and thyroid transcription factor (TFF1) [2,3].

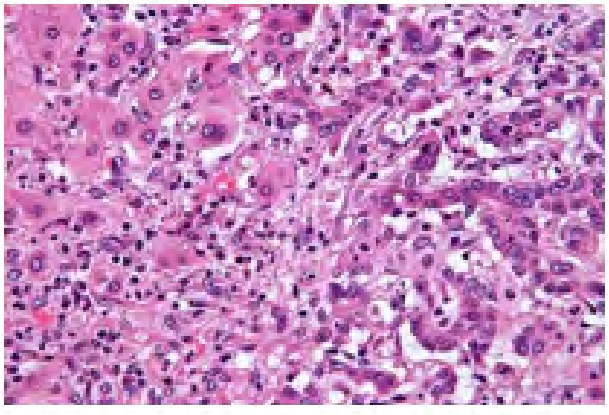

Figure 1: Intrahepatic cholangiocarcinoma depicting glandular articulations lined with atypical tall columnar epithelium with cellular and nuclear pleomorphism with intracytoplasmic lumens and intra-glandular cellular debris. Abutting foci of aggregated hepatocytes are discerned [6].

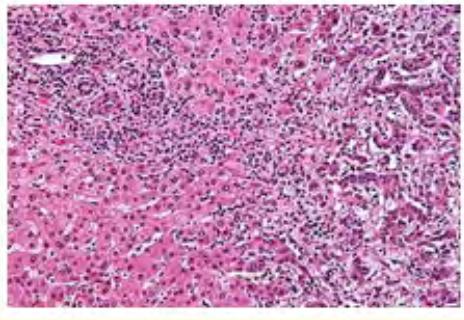

Figure 2: Intrahepatic cholangiocarcinoma delineating glandular structures lined with atypical tall columnar epithelium with cellular and nuclear pleomorphism, intracytoplasmic lumens and intra-glandular articulations. Adjacent foci of accumulated hepatocytes are discerned [7].

TNM staging of Intrahepatic Cholangiocarcinoma.

Primary tumour

- TX: Primary tumour cannot be assessed
- T0:No evidence of primary tumour
- Tis: Carcinoma in situ (intra-ductal tumour)
- T1a: Solitary tumour ≤5 centimetres with absence of vascular invasion
- T1b: Solitary tumour >5 centimetres with absence of vascular invasion
- T2: Solitary tumour with intrahepatic vascular invasion or multiple tumours along with or devoid of vascular invasion
- T3: Tumor perforating visceral peritoneum
- T4: Tumour involving local extrahepatic structures by direct invasion.

Regional lymph nodes

- NX: Regional lymph nodes cannot be assessed
- N0: Regional lymph node metastasis absent
- N1: Regional lymph node metastasis present

Left sided lesions incriminate regional lymph nodes as inferior phrenic, hilar or gastro-hepatic nodes whereas right sided lesions incriminate regional lymph nodes as hilar, periduodenal or peripancreatic nodes.

Distant metastasis

- M0: Distant metastasis absent
- M1: Distant metastasis present
- pM1: Distant metastasis confirmed upon microscopy [3,4]

Stages of Intrahepatic Cholangiocarcinoma as per American Joint Committee on Cancer (AJCC) 8th edition

- Stage 1A: T1a, N0,M0
- Stage IB: T1b,N0,M0
- Stage II: T2,N0,M0
- Stage IIIA: T3,N0,M0
- Stage IIIB: T4 and/or N1,M0
- Stage IV: Any T, any N,M1 [3,4].

Intrahepatic cholangiocarcinoma is immune reactive to CK7, CK17, CK19, CAM5.2, MOC31, epithelial membrane antigen

(EMA), monoclonal carcinoembryonic antigen (CEA), polyclonal carcinoembryonic antigen (CEA), claudin4 pVHL, albumin, glypican3 and HepPar1.

Intrahepatic cholangiocarcinoma is immune non reactive to CK20, TTF1, napsin A, oestrogen receptor (ER),progesterone receptor (PR) or GATA3 [4,5].

Intrahepatic cholangiocarcinoma requires segregation from neoplasms such as metastatic adenocarcinoma, hepatocellular carcinoma, combined hepatocellular cholangiocarcinoma, benign bile ductular reactions, epithelioid hemangioendothelioma, bile duct adenoma, choledocholithiasis, carcinoma pancreas, primary sclerosing cholangitis, primary biliary cirrhosis, cholangitis, cholecystitis, secondary sclerosing cholangitis, recurrent pyogenic cholangitis, acquired immunodeficiency syndrome (AIDS) associated cholangiopathy, autoimmune pancreatitis-cholangitis syndrome, hepatobiliary inflammatory pseudo-tumour, Mirizzi syndrome, xanthogranulomatous cholecystitis or cholangitis, biliary sarcoidosis, chemotherapy-induced biliary sclerosis or intra-biliary metastasis [4,5].

Appropriate clinical and pathological tumour discernment may be obtained with concurrence of radiological, biochemical and histological assessment. Generally, evaluation of hepatic parenchyma for malignant neoplasms and diverse pathologies is necessitated.

Assessment for possible occurrence of or screening for colorectal carcinoma, consumption of alcohol, travel history with possible infestation by liver flukes, serological assessment of viral hepatitis, autoimmune hepatitis, serum iron studies for excluding hemochromatosis and serum copper studies for excluding Wilson's disease is mandated.

Body mass index (BMI) may indicate the presence of non alcoholic steatohepatitis (NASH). Exposure to hepatotoxins as thorotrast or aflatoxin requires exclusion.

Assays of serum CA19-9, carcinoembryonic antigen (CEA) or alfa fetoprotein (AFP) are recommended. Generally, serum CA19-9 and serum CA125 levels are elevated. Besides, serum alkaline phosphatase and serum bilirubin levels appear variably increased [4,5].

Upon computerized tomography (CT), a singular, enlarged, homogeneous tumefaction with irregular perimeter is encountered. However, pathognomonic features of intrahepatic cholangiocarcinoma appear absent upon computerized tomography (CT) or magnetic resonance imaging (MRI).

Tumefaction may delineate progressive delayed image enhancement, peripheral rim enhancement or sub-capsular retraction [4,5].

Surgical eradication is a potential, curative therapy optimally applicable to intrahepatic cholangiocarcinoma. Frequently, neoplasm is inoperable and tumour reoccurrence following surgical intervention is encountered.

First line chemotherapy with gemcitabine or cisplatin can be adopted for treating locally advanced or metastatic neoplasms [4,5].

National Comprehensive Cancer Network (NCCN) recommends molecular evaluation of metastatic tumours or neoplasms unamenable to resection wherein> 50% of individuals subjected to next generation sequencing (NGS) depict potentially actionable chromosomal mutations.

Conclusion: Clinical trials of targeted therapy applicable to intrahepatic cholangiocarcinoma with immune checkpoint inhibitors (anti-PD1, anti-PDL1, anti-CTLA4 antibodies), IDH1 inhibitors, AKT / PI3K / mTOR inhibitors, FGFR inhibitors and anti-EGFR or MEK inhibitors are ongoing [4,5].

Factors contributing significantly to prognostic outcomes appear as ~serum carcinoembryonic antigen (CEA) levels

- CA 19-9 levels
- Quantifiable neoplasms
- Tumour magnitude
- Regional lymph node metastasis
- Vascular invasion
- Direct tumour invasion
- Localized extrahepatic metastasis
- Periductal tumour infiltration
- Tumour stage as per American Joint Committee on Cancer (AJCC) [4,5].

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6. Image 1 Courtesy: Wikipedia.

7. Image 2 Courtesy: Libre Pathology.