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The Native Flip-Flop-Intrahepatic Papillary Neoplasm of Bile Duct

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Abstract

Intrahepatic papillary neoplasm of bile duct configures as a papillary neoplasm with a distinct fibro-vascular stalk layered by variant epithelium pervading intrahepatic bile ducts with cystic dilatation. Neoplasm configures as a premalignant lesion associated with low grade, intermediate grade or high grade intraepithelial neoplasia. Tumour progression is concordant with preliminary inactivation of TP53 and p16, antecedent activating mutations within KRAS and delayed loss of SMAD4/ DPC4 gene. Cogent clinical symptoms arising due to biliary obstruction as hyper-bilirubinaemia or abdominal pain may emerge. Cytological smears are hyper-cellular and comprised of broad, double layered sheets and aggregates of columnar epithelial cells enmeshed within a fine stroma commingled with complex, three dimensional, branching papillary configurations. Morphologically, complex tubulovillous structures or micropapillary articulations appear to distend bile ducts or enlarged, multi-locular cysts are layered by pancreaticobiliary, intestinal, gastric or oncocytic epithelium.

Keywords: Papillary; Premalignant; Variant Epithelium; Bile Duct; Hepatolithiasis

Abbreviations: WHO: World Health Organization; IPNB: Intraductal Papillary Neoplasm of Bile-duct; IPMN: Intraductal Papillary Mucinous Neoplasm; EMA: Epithelial Membrane Antigen; MRI: Magnetic Resonance Imaging; CT: Computerized Tomography.

Introduction

Intrahepatic papillary neoplasm of bile duct configures as a papillary neoplasm pervading intrahepatic bile ducts demonstrating cystic dilatation. Tumefaction is constituted of a distinct fibro-vascular stalk layered by variant epithelium. Additionally designated as biliary papillomatosis or biliary papilloma, intraductal papillary neoplasm of bile duct emerges as a papillary neoplasm confined to distended intrahepatic bile ducts. Neoplasm appears devoid of ovarian stroma. As per contemporary classification of World Health Organization (WHO), intraductal papillary neoplasm of bile duct configures as a premalignant lesion delineating an intraductal papillary neoplasm associated with low grade, intermediate grade or high grade intraepithelial neoplasia. Alternatively, malignant neoplasm articulates as an intraductal papillary neoplasm with associated invasive carcinoma. The lesion depicts a significant proportion (~74%) of concordant invasive carcinoma. A male preponderance is observed. Pre-eminently, tumefaction is encountered within 50 years to 70 years and implicates individuals residing in Far East countries as Taiwan, Japan or Korea [1,2].

Intraductal papillary neoplasm of bile ducts commonly incriminates intrahepatic bile ducts. However, identical lesions may appear within extrahepatic bile ducts, pancreas or gallbladder. Frequently, tumefaction is multifocal [1,2]. Neoplasm may arise concurrent to disorders such as hepatolithiasis or infestation with clonorchis sinensis or liver fluke [1,2]. Neoplasm may depict gradual progression

from low grade dysplasia into high grade dysplasia and invasive carcinoma. Neoplastic evolution is concordant with preliminary inactivation of TP53 and p16, antecedent activating mutations within KRAS and delayed loss of SMAD4/DPC4 gene [2,3]. Intraductal papillary neoplasm of bile duct is associated with clinical symptoms arising due to biliary obstruction as hyper-bilirubinaemia or abdominal pain [2,3]. Cytological examination exhibits hyper-cellular smears comprised of broad double layered sheets and aggregates of columnar epithelial cells. Tumour cell component is enmeshed within a fine stroma commingled with complex, three dimensional, branching papillary configurations [2,3].

Grossly

A soft, friable, villiform tumefaction is encountered. The villi may be pedunculated, sessile or polypoid [3,4]. Upon microscopy, the papillary neoplasm demonstrates complex tubulovillous structures or micropapillary articulations. Neoplasm appears to expand within distended bile ducts. However, a circumscribing ovarian-type stroma is absent [3,4]. Tumefaction may configure enlarged, multilocular cysts encompassed by attenuated fibrous tissue septa. Layering epithelium may configure as pancreaticobiliary, intestinal, gastric or oncocytic subtype of epithelium [3,4].

Tumefaction may be classified as

- Type I or pancreatic subtype which appears reminiscent of intraductal papillary mucinous neoplasm (IPMN) of the pancreas and is frequently discerned as an intrahepatic or hilar neoplasm.

- Type II or non-pancreatic subtype of intraductal papillary neoplasm of bile duct (IPNB) where in type II subtype frequently emerges as an aggressive, extrahepatic lesion which is commonly associated with invasive carcinoma [3,4] (Figures 1 & 2).

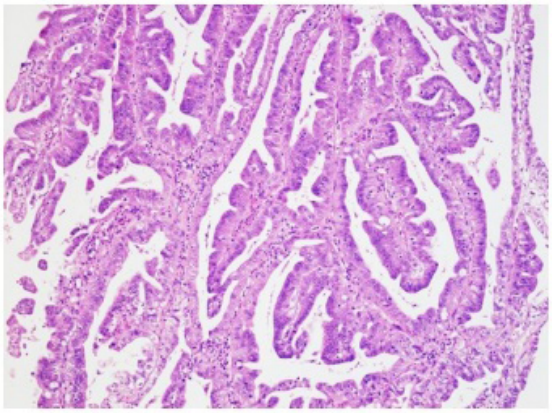

Figure 1: Intraductal papillary neoplasm of bile ducts composed of micro-papillary articulations with s distinct fibro-vascular stalk layered by intestinal epithelium with minimal cytological atypia [5].

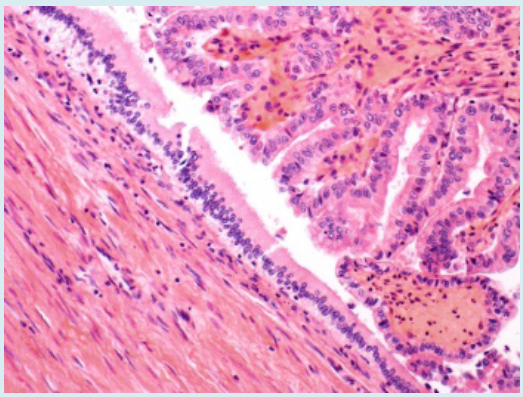

Figure 2: Intraductal papillary neoplasm of bile duct delineating micro-papillary articulations with a distinct fibro-vascular core layered by intestinal epithelium with minimal cytological atypia [6].

TNM Staging of Hepatocellular Carcinoma

Primary Tumour

- TX: Primary tumour cannot be assessed
- T0: No evidence of primary tumour
- T1: Solitary tumour <2 centimetres or > 2 centimetres with absent vascular invasion
- T1a: Solitary tumour < 2 centimetre magnitude
- T1b: Solitary tumour >2 centimetres with absent vascular invasion
- T2: Solitary tumour > 2 centimetres with vascular invasion or multiple tumours <5 centimetres magnitude
- T3: Multiple tumours with minimally a singular lesion >5 centimetres
- T4: Singular tumour or multiple tumours of variable magnitude incriminating major branch of portal vein or hepatic vein OR tumours with direct infiltration into adjacent viscera excluding gall bladder or perforation of visceral peritoneum [3,4].

Regional Lymph Nodes

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

Distant Metastasis

- M0: Distant metastasis absent
- M1: Distant metastasis present

Anatomic Staging of Hepatocellular Carcinoma

- stage IA: T1a, N0,M0
- stage IB: T1b, N0, M0
- stage II: T2, N0,M0
- stage IIIA: T3, N0, M0
- stage IIIB: T4, N0, M0
- stage IVA: Any T, N1, M0
- stage IVB: Any T, any N, M1

Histological Grading of Hepatocellular Carcinoma

- GX: Tumour grade cannot be assessed
- G1:Tumour is well differentiated
- G2: Tumour is moderately differentiated
- G3: Tumour is poorly differentiated
- G4: Tumour is undifferentiated

Intraductal papillary neoplasm of bile duct appears immune reactive to diverse mucins contingent to epithelial differentiation ~gastric type epithelium is immune reactive to MUC5AC and MUC6 ~intestinal type epithelium is immune reactive to MUC2 ~pancreatobiliary type epithelium appears immune reactive to MUC1 and epithelial membrane antigen (EMA) [7,8]. Stromal cells appear immune non-reactive to oestrogen or progesterone receptors. Invasive component of intraductal papillary neoplasm of bile ducts appears immune non-reactive to SMAD4 or DPC4 [7,8]. Intraductal papillary neoplasm of bile duct requires segregation from tumours as mucinous cystic neoplasm, cholangiocarcinoma, metastatic carcinoma, especially distant metastasis from colorectal adenocarcinoma, biliary intraepithelial neoplasia, simple cyst or intraductal tubulopapillary neoplasm of the bile duct [7,8].

Intraductal papillary neoplasm of bile ducts can be appropriately ascertained by imaging techniques as ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI) [7,8]. Neoplasm may be appropriately alleviated by surgical eradication of lesion. However, extensive tissue sampling with cogent histological evaluation is necessitated in order to discern invasive component and exclude tumour invasion [7,8]. Neoplasms associated with biliary obstruction may delineate elevated levels of serum bilirubin and serum alkaline phosphatase. Ultrasonography, computerized tomography (CT) or magnetic resonance imaging (MRI) may aptly detect morphological features as dilatation of bile ducts or occurrence of intraductal tumefaction [7,8]. Optimal mode of therapy is surgical extermination of the neoplasm. Additionally, palliative therapeutic approaches as chemotherapy or laser ablation of the neoplasm can be beneficially employed [7,8]. Emergence of an invasive component within intraductal papillary neoplasm of bile duct is associated with decimated overall survival, contingent to proportion and depth of neoplastic invasion. Multiple lesions or disseminated neoplasms display inferior prognostic outcomes wherein appropriate alleviation of aforesaid disease may be challenging [7,8].

Conclusion

Intraductal papillary neoplasm of bile duct appears immune reactive to diverse mucins wherein gastric type epithelium is immune reactive to MUC5AC and MUC6, intestinal type epithelium is immune reactive to MUC2 and pancreatobiliary type epithelium appears immune reactive to MUC1 and epithelial membrane antigen. Stromal cells are immune non-reactive to oestrogen or progesterone receptors whereas invasive component is immune non-reactive to SMAD4 or DPC4. Intraductal papillary neoplasm of bile duct requires segregation from tumours as mucinous cystic neoplasm, cholangiocarcinoma, metastatic carcinoma, especially distant metastasis from colorectal adenocarcinoma, biliary intraepithelial neoplasia, simple cyst or intraductal tubulopapillary neoplasm of the bile duct.

Tumefaction can be appropriately ascertained by imaging techniques as ultrasonography, computerized tomography (CT) and magnetic resonance imaging (MRI). Neoplasm may be appropriately alleviated by surgical eradication.

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5. Image 1 Courtesy: Research gate

6. Image 2 Courtesy: Pathology outlines

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