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Editorial

Deep-rooted and Inherent-Intracholecystic Papillary Neoplasm

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Intracholecystic papillary neoplasm emerges as a macroscopically discernible, non invasive epithelial neoplasm configuring as mass confined to gallbladder mucosa or a tumour projection into lumen of gallbladder. Initially scripted by Adsay et al in 2012, the neoplasm is contemplated as a distinct subtype of pre invasive neoplasm of gallbladder, as per the contemporary World Health Organization (WHO) classification 2019 [1].

Preceding terminology of biliary adenoma, papillary adenoma, tubulopapillary adenoma, intracystic papillary neoplasm, intracholecystic papillary tubular neoplasm or papillary carcinoma is not recommended.

Intracholecystic papillary neoplasm (ICPN) appears reminiscent of intraductal papillary mucosal neoplasm of pancreas as the tumefaction expounds a spectrum of morphological configurations, variable cellular lineage and a frequent admixture of various histological articulations along with dysplastic modifications. Generally, tumour magnitude is ≥ 1 centimetre. Microscopy depicts papillary, tubular or tubulopapillary neoplastic patterns wherein distinct morphological articulations as biliary, intestinal, gastric and oncocytic are encountered. Neoplasm may concur with foci of invasive carcinoma.

Mean age of disease emergence is 61 years. A female preponderance is encountered with female to male proportion of 2:1. Lesion may be incidentally discovered in < 1% of cholecystectomies [2,3].

Intracholecystic papillary neoplasm demonstrates genomic mutations within KRAS, STK11, CTNNB1 and APC genes whereas chromosomal mutations within TP53 and GNAS genes are exceptional [2,3].

The neoplasm is commonly confined to fundus and body of gallbladder.

Of obscure aetiology, neoplasm appears non concurrent with conditions as cholelithiasis [2,3].

Intracystic papillary neoplasm may be discovered incidentally. Alternatively, lesion may represent with pain confined to right upper quadrant [2,3].

Grossly, solitary or multifocal lesions may display a preponderant exophytic pattern of neoplastic evolution. Alternatively, granular, friable, soft excrescences of tan hue may be confined to the gall bladder.

Intraluminal friable excrescences appear loosely adherent and may be misinterpreted as sludge or debris confined to the gallbladder lumen on account of inadequate sampling during preliminary macroscopic evaluation. Median tumour magnitude emerges at 2.2 centimetres [3,4].

Upon microscopy, densely aggregated units of epithelial glands appear to configure papillary, tubular or tubule-papillary articulations with minimal intervening stroma.

Distinct morphological subtypes appear as ~biliary phenotype is commonly encountered and characteristically depicts papillary articulations layered by cuboidal epithelial cells imbued with clear to eosinophilic cytoplasm, enlarged nuclei and distinct nucleoli. Proportionate emergence of associated invasive carcinoma is significant. Additionally, gastric phenotype and pyloric subtype may be encountered [3,4].

Intracholecystic papillary neoplasms typically depict a dense collection of mucinous glands of gastric pyloric glandular phenotype.

Contemporary World Health Organization (WHO) classification 2019 describes subtypes of intracholecystic papillary neoplasm as a distinct entity, in contrast to pyloric gland adenoma which is a variant associated with minimal possible emergence of associated invasive carcinoma gallbladder [3,4].

- Foveolar phenotype depicts enlarged, elongated glands layered by tall columnar, mucinous epithelium wherein epithelial cells are imbued with pale cytoplasm.
- Intestinal phenotype morphologically simulates colonic adenoma wherein layering columnar epithelial cells delineate significant cytoplasmic basophilia and pseudostratified cigar shaped nuclei.
- Oncocytic phenotype is infrequently discerned and typically displays arborizing papillary articulations layered by enlarged oncocytic cells imbued with granular cytoplasm and prominent, enlarged, eccentric nucleoli. Cellular atypia may be encountered [3,4].

Notwithstanding, admixture of aforesaid phenotypes is encountered.

Characteristically, neoplasms layered by epithelial cells impregnated with abundant cytoplasm, miniature, uniform nuclei and distinct nucleoli are categorized as lesions with low grade dysplasia. Lesions displaying complex architecture and nuclear atypia appear to expound high grade dysplasia.

Non invasive neoplasms necessitate cogent determination of presence and quantity of high grade dysplasia.

An estimated >50% lesions depict associated invasive carcinoma upon initial tumour discernment, a feature which is predominantly encountered in lesions of biliary phenotype and high grade dysplasia [5,6].

Associated invasive carcinoma preponderantly emerges as pancreatobiliary subtype of adenocarcinoma. Additionally, variants as colloid carcinoma or poorly differentiated neuroendocrine carcinoma may be enunciated. Invasive carcinoma is macroscopically non discernible and may arise at a site distant to initial lesion. Thus, meticulous tissue sampling and thorough microscopic evaluation are beneficial and recommended [5,6].

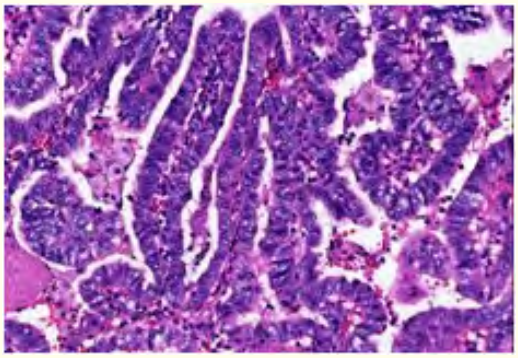

Figure 1: Intracholecystic papillary neoplasm demonstrating papillae layered by columnar epithelium with minimal cellular and nuclear atypia. Intervening stroma is minimal [11].

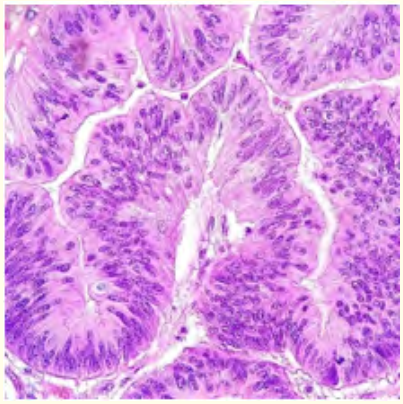

Figure 2: Intracholecystic papillary neoplasm delineating papillary structures lined by pseudostratified columnar epithelium with minimal cytological atypia. Intervening stroma is minimal [12].

Staging modality of Barcelona clinic liver cancer (BCLC) is constituted of

- Performance status
- Child-Pugh score
- Tumour extent upon radiography
- Tumour magnitude
- Multiplicity of tumours
- Vascular invasion
- Regional lymph node involvement
- Extrahepatic metastases [3,4].

Contingent to aforesaid parameters, hepatocellular carcinoma is categorized as

- Stage 0 comprised of preliminary tumour stage or asymptomatic preliminary tumours with performance status (PS) 0, Child-Pugh A and a solitary lesion <2 centimetre magnitude. Neoplasm can be managed with singular surgical resection. Tumefaction associated with portal hypertension or hyperbilirubinemia is optimally subjected to liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation.
- Stage A comprised of preliminary tumour stage or asymptomatic antecedent neoplasms with performance status (PS) 0 to 2, Child-Pugh A to C and a solitary lesion >2 centimetre diameter or antecedent multifocal disease with characteristically up to three lesions < 3 centimetre magnitude. Singular neoplasms can be subjected to surgical resection. Multiple lesions are managed with liver transplantation. Tumours associated with diverse clinical comorbidities are appropriately alleviated with radiofrequency ablation.
- Stage B or intermediate stage is comprised of asymptomatic multifocal disease with performance status (PS) 0, Child-Pugh A to C, multifocal disease with ≥ 1 lesion and minimally a singular lesion > 3 centimetre diameter or > 3 lesions irrespective of tumour magnitude. Neoplasm is optimally treated with transcatheter arterial chemoembolization (TACE).
- Stage C or advanced stage is constituted of symptomatic neoplasm associated with tumour invasion and/or distant metastasis with performance status (PS) 1 to 2, Child-Pugh A to C, vascular invasion and/or regional lymph node disease and/or distant metastasis. Neoplasm is managed with varieties of palliative therapy and agents as sorafenib or phase II trial agents.
- Stage D or end-stage disease configures as a terminal stage and enunciates performance status (PS) >2, Child-Pugh C and appears singularly as a clinical stage. Optimally, symptomatic therapeutic options are beneficial. Tumour stage is compatible with Okuda stage III [3,4].

Intracholecystic papillary neoplasm demonstrates immune reactivity designated as

- Biliary phenotype is reactive to CK7 or MUC1
- Intestinal phenotype appears immune reactive to CK20, CDX2, MUC2
- Foveolar phenotype is immune reactive to MUC5AC
- Pyloric phenotype appears immune reactive to MUC6
- Oncocytic phenotype appears immune reactive to MUC1 or HepPar1 [5,6].

Intracholecystic papillary neoplasm requires segregation from tumefaction as pyloric gland metaplasia or intracholecystic tubular non mucinous neoplasm (ICTNs) [7,8].

Contrast enhanced imaging upon computerized tomography (CT) and magnetic resonance (MR) cholangiopancreatography characteristically depicts a tumour-like defect within the gallbladder in concurrence with dilatation of upstream bile duct. Upon radiography, an estimated 50% neoplasms are misinterpreted as carcinoma gallbladder [7,8].

Intracholecystic papillary neoplasm is pre-eminently managed with cogent surgical eradication of the neoplasm [9,10].

Despite concurrence with invasive carcinoma, overall prognostic outcomes are favourable. Intracholecystic papillary neoplasm associated invasive carcinomas configure as indolent neoplasms delineating superior prognostic outcomes, in contrast to conventional or pancreatobiliary subtype of gallbladder carcinomas [9,10].

Neoplasms with papillary configuration, biliary subtype or foveolar phenotype and lesions associated with high grade dysplasia contribute significantly to emergence of associated invasive carcinomas of gallbladder [9,10].

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11. Image 1 Courtesy: Pathology outlines.

12. Image 2 Courtesy: Journal of current surgery.