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Editorial

Ingenerate and Switched - Biliary Intraepithelial Neoplasia

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Biliary intraepithelial neoplasia configures as a premalignant, neoplastic, microscopic lesion confined to gallbladder or bile duct epithelium. The pre-eminently morphological lesion appears devoid of invasion into circumscribing stroma.

Contemplated as a biliary counterpart of pancreatic intraepithelial neoplasia, the lesion is categorized contingent as discernible, proportionate cytological atypia.

Additionally designated as biliary dysplasia or carcinoma in situ, the configured non mass forming lesion is layered with flattened epithelium or micro-papillary articulations. Layering epithelium demonstrates low grade dysplasia or high grade dysplasia.

Biliary intraepithelial neoplasia is commonly associated with lithiasis and may be incidentally discovered within surgical specimens obtained with elective cholecystectomy.

Biliary intraepithelial neoplasia associated with high grade dysplasia may be appropriately alleviated by surgical extermination of the lesion. Thus, prognostic outcomes are superior.

A specific gender predilection is absent. Biliary intraepithelial neoplasia commonly incriminates the gallbladder, intrahepatic biliary tract or extrahepatic biliary tree [1,2].

Biliary intraepithelial neoplasia is posited to arise from perpetual inflammation and infiltration by chronic inflammatory cells. Besides, stimulation of biliary epithelium through diverse mechanisms induces neoplastic modifications along with contribution of various molecular pathways [1,2].

Biliary carcinogenesis demonstrates preliminary genomic mutations within KRAS genes in nearly 33% lesions. Notwithstanding, delayed molecular modifications concur with TP53 genetic mutations. The non mass forming lesion is postulated to concur with diseases as lithiasis, primary sclerosing cholangitis, choledochal cysts or anomalous configuration of pancreaticobiliary ductal articulations [1,2].

An estimated one third (~33%) of biliary intraepithelial neoplasia demonstrate genomic mutations within KRAS gene which configure as a preliminary molecular phenomenon during progression of lesion whereas overexpression of p53 emerges as a delayed molecular phenomenon. Additionally, molecules as p21, p53, cyclin D1 and DPC4 are implicated within carcinogenesis of biliary intraepithelial neoplasia [2,3].

The lesion is asymptomatic and devoid of cogent clinical representation. Generally, the lesion may be discerned within biliary mucosa abutting foci of invasive carcinoma [2,3].

Cytological assessment of biliary intraepithelial neoplasia appears challenging as the microscopic, non mass forming lesion may be unamenable to fine needle aspiration cytology [2,3].

Brush cytology of bile duct exhibits neoplastic cells pervaded with elevated nucleocytoplasmic ratio, enlarged nuclei, anisonucleosis, irregular nuclear perimeter, hyperchromatic nuclei and visible or prominent nucleoli. Pre-eminently, aforesaid alterations are associated with clonal somatic genomic mutations which may be precisely ascertained by next generation sequencing (NGS) [2,3].

Grossly, a distinct, identifiable lesion is absent. Incriminated mucosa is granular and velvety [3,4].

Upon microscopy, lesion expounds a preponderantly flattened mucosa. Alternatively, a micro-papillary or pseudo-papillary architecture is exemplified.

Low grade biliary intraepithelial neoplasia exhibits

- Lesion confined to miniature mucosal areas with sparing of peri-biliary glands
- Epithelial cells pervaded with hyperchromatic nuclei and uniform nuclear membrane
- Elevated nucleocytoplasmic ratio
- Stratification of nuclei
- Retained nuclear polarity

Mild to moderate enhancement of Ki67 proliferative index [3,4].

High grade biliary intraepithelial neoplasia enunciates

- Extensive involvement of mucosal zones and peribiliary glands
- Epithelial cells permeated with hyperchromatic nuclei delineating irregular nuclear membrane
- Significantly elevated nucleocytoplasmic ratio
- Extensive cellular and nuclear polymorphism with predominant nuclear atypia
- Complex stratification of nuclei
- Loss of nuclear polarity

Significantly augmented Ki67 proliferative index [3,4].
(Figure 1,2)

TNM staging of hepatocellular carcinoma [3,4].

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

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

Biliary intraepithelial neoplasia appears immune reactive to CK7, CK19, CK20, MUC1, MUC5AC, p53 and S100 protein.

Tumour cells appear immune non reactive to MUC2 and MUC6 [4,5].

Biliary intraepithelial neoplasia requires segregation from neoplasms as reactive alterations within the biliary tract or biliary tract adenocarcinoma [4,5].

Appropriate neoplastic discernment is obtained by cogent morphological evaluation of the lesion. Singular adoption of cytological assessment remains insufficient for segregating reactive epithelial alterations from pre-invasive lesions and invasive neoplasms.

Upon imaging, biliary intraepithelial neoplasia appears non discernible as the tumefaction represents as a non mass forming lesion [4,5].

Majority of high grade biliary intraepithelial neoplasia incriminating the gallbladder may be appropriately alleviated by cholecystectomy.

Factors contributing to inferior prognostic outcomes emerge as

- Extensive biliary disease
- Incrimination of Rokitansky-Aschoff sinuses
- Tumour confined to surgical margins.

Besides, aforesaid parameters enhance possible tumour reoccurrence [4,5].

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6. Image 1 Courtesy: Pathology outlines.

7. Image 2 Courtesy: American cancer society.