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The Mingled Allies-Combined Hepatocellular Carcinoma and Cholangiocarcinoma

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Editorial

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Abbreviations: WHO: World Health Organization; PCEA: Polyclonal Carcinoembryonic Antigen; EPCAM: Epithelial Cell Adhesion Molecule; AFP: Alpha Fetoprotein; CT: Computerized Tomography; CEA: Carcinoembryonic Antigen.

Editorial

Combined hepatocellular carcinoma and cholangiocarcinoma is an exceptionally discerned, primary malignant neoplasm incriminating the hepatic parenchyma. Neoplasm categorically exhibits an amalgamation of dual hepatocellular and biliary differentiation within a singular neoplasm. Notwithstanding, collision tumours do not configure as combined lesions.

The primary tumour incriminating hepatic parenchyma is constituted of homogenous population of bi-phenotypic tumour cells. Additionally designated as intermediate cell carcinoma, tumefaction is contemplated to be a subtype of combined hepatocellular carcinoma and cholangiocarcinoma.

As per the current classification of World Health Organization (WHO) 2019, cholangiolocellular carcinoma is categorized along with cholangiocarcinoma. Therefore, a neoplasm comprised of cholangiocellular carcinoma associated with hepatocellular carcinoma may be denominated as combined hepatocellular carcinoma and cholangiocarcinoma.

Neoplasm may be adequately ascertained by routine histopathological examination of formalin fixed, paraffin embedded sections stained with haematoxylin and eosin. Precise immunohistochemistry may be beneficially adopted as a concordant diagnostic modality. Notwithstanding, terminologies such as mixed hepatocellular-cholangiocarcinoma, mixed hepatobiliary carcinoma, hepato-cholangiocarcinoma or hepatocellular carcinoma-cholangiocarcinoma with stem cell features require circumvention.

The primary hepatic malignancy constituted of combined hepatocellular carcinoma and cholangiocarcinoma demonstrates categorical components of hepatocellular and biliary differentiation and configures< 1% of primary hepatic malignancies. Tumefaction is preponderantly intrahepatic [1,2].

Tumefaction is posited to emerge

- As an incidental coexistence of hepatocellular carcinoma and intrahepatic cholangiocarcinoma within a singular lesion
- Malignant transformation of hepatic progenitor cell
- Dedifferentiation of hepatocellular carcinoma or intrahepatic cholangiocarcinoma [1,2].

Factors contributing to emergence of hepatocellular carcinoma or intrahepatic cholangiocarcinoma appear to predispose towards occurrence of combined lesions and configure as

- Viral hepatitis
- Alcohol intake
- Non-alcoholic steatohepatitis [1,2].

Occurrence of hepatic cirrhosis in subjects with combined neoplasms demonstrates intermediate incidence between enhanced proportion with hepatocellular carcinoma and

decimated prevalence with intrahepatic cholangiocarcinoma [2,3].

However, cogent factors influencing emergence of the exceptionally encountered combined hepatocellular carcinoma and intrahepatic cholangiocarcinoma remain obscure [2,3].

Combined hepatocellular carcinoma and cholangiocarcinoma frequently exhibits genetic mutations within driver genes as TP53, TERT promoter region, AXIN1 or KMT2D [2,3].

Combined hepatocellular carcinoma and cholangiocarcinoma delineates a male predominance. Clinical symptoms are non-specific and appear as fatigue, obstructive jaundice, loss of weight or abdominal discomfort [2,3]. Grossly, neoplasm represents as a lobular, firm, well demarcated, un-encapsulated tumefaction delineating yellowish white patterned hue.

Upon microscopy, classical combined hepatocellular carcinoma and cholangiocarcinoma enunciates admixed foci of typical hepatocellular carcinoma and typical intrahepatic cholangiocarcinoma [3,4]. Foci of hepatocellular carcinoma delineate cytological and architectural features indicative of hepatocellular carcinoma. Intrahepatic cholangiocarcinoma emerges distinctly as an adenocarcinoma comprised of malignant glands encompassed within a dense, fibrotic stroma. Aforesaid components may be commingled or configure disparate foci within diverse tumour regions. Nevertheless, focal areas displaying merging of dual components are frequently discerned [3,4].

Notwithstanding, a definitive consensus for quantifiably minimal hepatocellular carcinoma component or intrahepatic cholangiocarcinoma component in order to categorize the neoplasm remains absent. Intermediate cell carcinoma enunciates a monomorphic neoplasm composed of tumour cells with magnitude between normal hepatocytes and stem progenitor cell phenotype [3,4].

Tumefaction configures cellular trabeculae, cords, solid nests or strands enmeshed within significantly desmoplastic or acellular, hyalinised stroma. Tumefaction may articulate elongated, inadequately defined, gland-like structures indicative of tubules. However, well defined glands are absent [3,4]. Tumour cells display morphological features intermediate between hepatocytes and cholangiocytes. Neoplastic cells appear as cuboidal to ovoid and are impregnated with pale or pink cytoplasm. Cellular atypia and mitotic activity are infrequent. Mucin production is absent [3,4].

Cholangiolocellular carcinoma may configure as a component of combined hepatocellular carcinoma and cholangiocarcinoma. However, singular cholangiocellular carcinoma represents as a subtype of intrahepatic cholangiocarcinoma (Figure 1) [3,4].

Cholangiocellular carcinoma simulates epithelial component of ductular reaction. Tumefaction is constituted of attenuated, malignant, ductular-like articulations which appear to radiate from or circumscribe portal tracts demonstrating a tubular, cord-like or anastomosing antler-like pattern. The cellular component is encompassed within dense, hyalinised stroma. Tumefaction may demonstrate trabeculae and layer the cellular growth interface within circumscribing non-tumorous hepatic parenchyma. Cholonagiocellular carcinoma is non-reactive to mucin (Figure 2 and Table 1) [3,4].

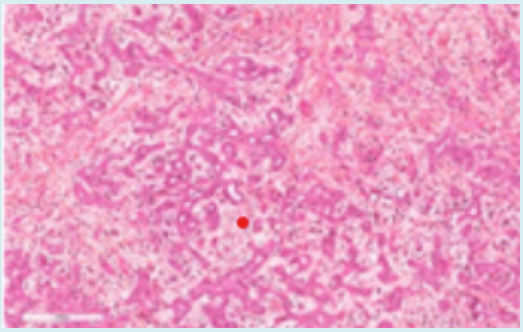

Figure 1: Combined hepatocellular carcinoma and cholangiocarcinoma composed of cuboidal cells impregnated with pale, pink cytoplasm, intermingled with glandular articulations layered with malignant epithelium and an encompassing fibrotic stroma [5].

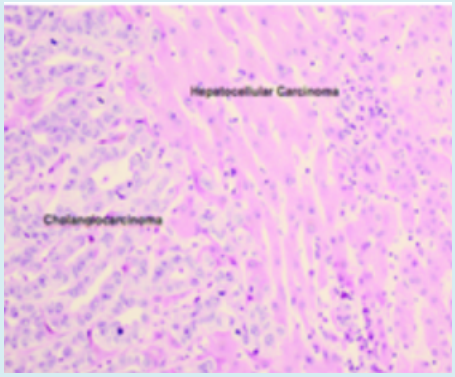

Figure 2: Combined hepatocellular and cholangiocarcinoma demonstrating cuboidal cells pervaded with abundant eosinophilic cytoplasm and commingled glandular structures layered with malignant epithelium and circumscribing fibrotic stroma [6].

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WHO classification 4th edition	WHO classification 5th edition
combined hepatocellular carcinoma and cholangiocarcinoma-classical type	combined hepatocellular carcinoma and cholangiocarcinoma -classical type
combined hepatocellular carcinoma and cholangiocarcinoma with stem cell features-classical type	intermediate cell carcinoma
combined hepatocellular carcinoma and cholangiocarcinoma with stem cell features- intermediate type	classified with cholangiocarcinoma
combined hepatocellular carcinoma and cholangiocarcinoma with stem cell features- cholangiocellular type	classified with cholangiocarcinoma

Table 1: Contemporary World Health Organization (WHO) classification of combined hepatocellular carcinoma and cholangiocarcinoma [1].

Precise immunohistochemistry exhibits a bi-phenotypic tumour. Tumour cells constituting hepatocellular carcinoma appear immune reactive to HepPar1, arginase glypican, polyclonal carcinoembryonic antigen (pCEA) or CD10 [7].

Cellular component of intrahepatic cholangiocarcinoma appears immune reactive to CK7, CK19 or epithelial cell adhesion molecule (EpCAM). Tumour cells comprising hepatocellular carcinoma appear immune non-reactive to alpha fetoprotein (AFP), CK7, CK19 or epithelial cell adhesion molecule (EpCAM) [7].

Cellular component of intrahepatic cholangiocarcinoma appears immune non-reactive to HepPar1, arginase1, polyclonal carcinoembryonic antigen (pCEA), CD10, alpha fetoprotein (AFP) or glypican 3 [7]. Combined hepatocellular carcinoma and cholangiocarcinoma requires segregation from neoplasms such as hepatocellular carcinoma or intrahepatic cholangiocarcinoma [7].

Preoperative discernment of the neoplasm is challenging as the lesion is devoid of cogent features upon non-invasive imaging. Nevertheless, tumefaction may exhibit concurrent features between hepatocellular carcinoma and intrahepatic cholangiocarcinoma.

Upon imaging, neoplasm appears heterogeneous and demonstrates concurrent features between hepatocellular carcinoma and intrahepatic cholangiocarcinoma. Quantifiable component of aforesaid neoplasms appears concordant with radiological features [7].

Upon computerized tomography (CT), tumours with predominant hepatocellular carcinoma delineate an intense contrast uptake during arterial phase with a washout within the venous phase. Neoplasms with preponderant intrahepatic cholangiocarcinoma exemplify progressive centripetal enhancement, retraction of capsule or peripheral rim enhancement [7].

Generally, serum alpha fetoprotein levels exceed > 400ng/ml. Hepatocellular carcinoma exhibits elevated serum CA19-9 levels whereas intrahepatic cholangiocarcinoma is accompanied by decimated values of serum CA19-9. Nearly 25% neoplasms enunciate increased levels of carcinoembryonic antigen (CEA).

Precise histological examination following extensive tumour and tissue sampling of surgical resection specimens appears confirmatory [7]. Combined hepatocellular carcinoma and cholangiocarcinoma is devoid of standardized therapeutic regimen applicable for alleviation of neoplasm. Optimal curative modality emerges as surgical extermination of neoplasm along with regional lymph node dissection. Therapeutic employment of liver transplantation is contraindicated. Localized and regional therapeutic strategies as arterial chemoembolization, radiofrequency or systemic chemotherapy may be adopted for neoplasms unamenable to surgical resection [7].

Factors contributing to unfavourable prognostic outcomes emerge as

- Enlarged tumour magnitude > 5 centimetres
- Occurrence of satellite tumour nodules
- Metastasis into regional lymph nodes
- Vascular tumour invasion
- Infiltration of portal vein
- Enhanced tumour stage
- Tumour free surgical margins < 2 centimetres [7].

In contrast to hepatocellular carcinoma, a prognostic outcome of combined neoplasms is inferior and appears identical to outcomes of intrahepatic cholangiocarcinoma. Following surgical intervention, proportionate tumour reoccurrence appears at ~80% at 5 years [7].

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5. Image 1 Courtesy: Pathology outlines.

6. Image 2 Courtesy: Research gate.

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