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*MINIREVIEWS*

# Solid-Tubulocystic carcinoma: A new variant of intrahepatic cholangiocarcinoma

Iván A González, Wenyi Luo, Xuchen Zhang

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## Abstract

A new variant of intrahepatic cholangiocarcinoma (iCCA) has been recognized in recent years presenting predominantly as a large hepatic mass in young woman with the characteristic expression of inhibin by immunohistochemistry. This variant iCCA was originally termed as cholangioblastic variant of iCCA, and subsequently proposed to be renamed as inhibin-positive hepatic carcinoma or solid-tubulocystic variant of iCCA to better reflect its immunohistochemical profile or morphologic spectrum. The tumor histologically is composed of small to medium sized cells with scant to moderate amount of eosinophilic cytoplasm heterogeneously organized in solid, tubular, and cystic growth patterns. The tumor cells are positive for biliary markers, inhibin and albumin, and have a novel recurrent gene fusion, *NIPBL::NACC1*. Awareness of this new iCCA variant and its clinicopathologic features will aid in the diagnostic work-up and avoid confusion with other primary and metastatic hepatic neoplasms.

**Key Words:** Cholangiocarcinoma; Intrahepatic; Solid-tubulocystic; Cholangioblastic; Inhibin

**Core Tip:** Solid-tubulocystic variant of intrahepatic cholangiocarcinoma (iCCA) is a recently recognized iCCA variant, which previously was termed as cholangioblastic iCCA. This new variant iCCA predominantly presents in young woman characterized by a heterogenous microscopic appearance with small to medium sized tumor cells with eosinophilic cytoplasm organized in solid, tubular, and cystic growth patterns. One of the defining features is the diffuse expression of inhibin. Recurrent *NIPBL::NACC1* gene fusion has been identified in this iCCA variant. Compared to typical iCCAs, patients with this variant iCCA may have a better prognosis with 25% of the cases reported died of disease in 5 years.

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## INTRODUCTION

Cholangiocarcinoma (CCA) is a highly aggressive adenocarcinoma arising from the biliary tree and can be divided into intrahepatic CCA (iCCA), perihilar CCA and distal CCA. Perihilar CCA arises from the second-order bile ducts to the insertion of the cystic duct whereas distal CCA is confined to the common bile duct below this insertion[1,2]. Collectively perihilar and distal CCA are referred as extrahepatic CCA. The most recent WHO classification of the digestive system tumours classified iCCA into two main subtypes based on their histologic features, small duct and large duct[3]. Other recognized rare variants of iCCA include adenosquamous carcinoma, squamous carcinoma, mucinous carcinoma, mucoepidermoid carcinoma, signet-ring cell carcinoma, clear cell carcinoma, ductal plate malformation-like pattern carcinoma, lymphoepthelioma-like carcinoma and sarcomatous carcinoma[3,4]. Recently, a new variant of inhibin-positive iCCA has been reported, which was termed as solid-tubulocystic or cholangioblastic variant iCCA[5-10]. This novel variant has a characteristic gene fusion, *NIPBL::NACC1*, which was first recognized by Argani *et al*[7], and subsequently confirmed in another case report by González *et al*[5].

This mini review summarized the unique clinical, morphologic, and molecular features of this newly identified and underrecognized inhibin-positive solid-tubulocystic/cholangioblastic variant iCCA. Awareness of this new variant would aid practicing physicians to recognize this rare variant iCCA.

## CLINICAL FEATURES

The inhibin-positive solid-tubulocystic variant iCCA presents with a median age of 28 years (range: 15-54 years) and predominantly occurs in woman (82%)[5-9,11-13]. The majority of the patients presents with non-specific abdominal distention and pain as well as nausea, vomiting and discomfort. On imaging the tumor is characterized by a heterogenous appearance with both solid and cystic areas and tends to have a well-demarcated border[5]. The median size at presentation is 16 cm (range: 6.9-32 cm). Of the patients reported with available follow-up information, half of the patients developed recurrence or metastasis during follow-up which were treated with adjuvant chemotherapy, and 25% (4 cases) died of disease all within 5 years of diagnosis.

## MORPHOLOGIC FEATURES

The inhibin-positive solid-tubulocystic/cholangioblastic variant iCCA has distinct and characteristic morphologic features with multiple different patterns recognized within each tumor. Grossly, the tumors are well-circumscribed and the cut-surfaces vary from a solid tan-white to tan-yellow surface with areas of hemorrhage and degeneration[5]. Tumor necrosis is often seen particularly in larger tumors. Areas with a multicystic surface creating a spongiform appearance in some cases can be seen[5]. These cystic structures often have smooth inner surface and are filled with clear to tan-yellow fluid. In some cases, fibrous bands can be seen within the tumor.

As one could expect from the heterogenous gross appearance, the histologic features of this tumor vary in different areas within the same tumor which is both useful in their diagnosis but can also create confusion and a potential misdiagnosis. The solid areas are characterized by tumor cells with scant to moderate amount of eosinophilic focally granular cytoplasm with round to oval nuclei with a finely granular chromatin and occasional small nucleoli (Figures 1A and B). These tumor cells are organized in solid sheets to trabecular growth patterns and tubular/pseudoglandular structures. Both the cytologic morphology and architectural configuration are reminiscent of well-differentiated neuroendocrine tumors (WD-NET) and acinar cell carcinomas (ACC) which are differential diagnoses of these tumors. In other areas a tubular architecture is seen with cystic dilatation. The cysts are lined by tumor cells with similar cytologic features as the solid areas, and pink colloid-like secretions can be seen within the lumen in some cases mimicking thyroid follicular neoplasm. In some cases, the compact solid areas have a more crowded pattern with tumor cells showing only scant cytoplasm. Given this appearance these tumor cells are considered as a more "primitive" appearance and referred as

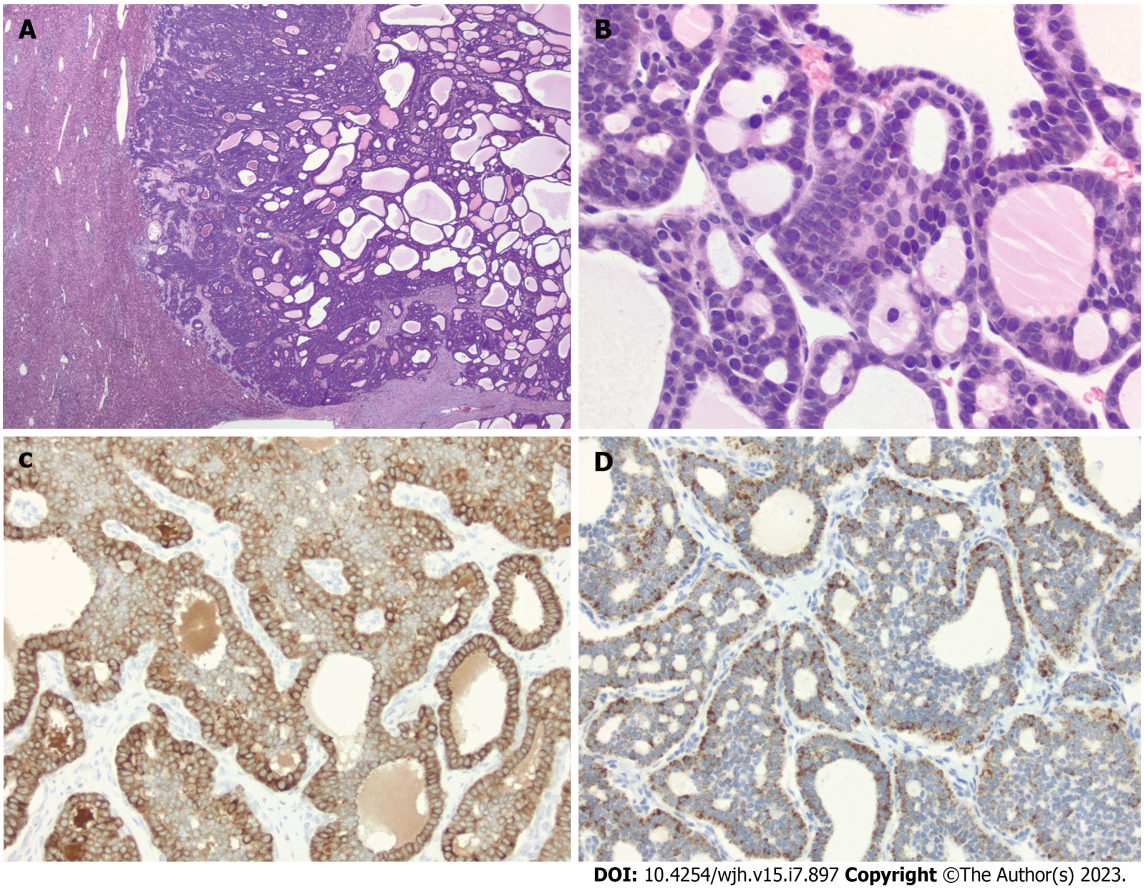


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**Figure 1 Solid-tubulocystic variant of intrahepatic cholangiocarcinoma.** A: Representative picture of a resected solid-tubulocystic variant of intrahepatic cholangiocarcinoma (right) in a non-cirrhotic liver (left). The tumor is well demarcated from the background liver (20x, Hematoxylin-eosin stain); B: Representative picture showing the tumor with solid, tubular, and cystic growth patterns (200x, Hematoxylin-eosin stain); C: Representative picture showing the tumor cells are positive for inhibin (200x, immunohistochemical stain); D: Representative picture showing tumor cells are positive for albumin (200x, in situ hybridization).

blastema-like areas. Therefore, these lesions have been termed as "cholangioblastic variant of iCCA" given the presence of blastema-like areas and the expression of neuroendocrine markers, a common feature of other primitive tumors[6]. However, in our opinion these tumors do not have the characteristics of other primitive epithelial tumors, nor recapitulate the developing ductal plate[5]. In light of this and the histologic features, we prefer to use the term of solid-tubulocystic variant of iCCA as proposed by Wen KW and colleagues[8], instead of cholangioblastic variant of iCCA.

## IMMUNOPHENOTYPE

Perhaps given the rarity of this variant iCCA, an extensive immunophenotype has been reported in the case report and small case series in the literature with the most characteristic finding being the diffuse and strong expression of inhibin (Table 1) (Figure 1C)[5-9,11,14]. As expected, the tumor is diffusely positive for cytokeratin (CK) AE1/AE3, CAM5.2, CK7 and CK19, whereas being negative for CK20 and CDX2, consistent with a biliary phenotype. It is also negative for hepatocellular markers, such as HepPar1 and arginase-1. Of note, albumin by in situ hybridization is positive in tumor cells (Figure 1D), which is consistent with primary hepatic carcinoma - iCCA. One of the pitfalls is the focal to diffuse expression of multiple neuroendocrine markers including CD56, synaptophysin and chromogranin, which varies from a weak to strong positivity, but INSM1, a more specific neuroendocrine marker is so far reported to be negative.

## MOLECULAR FEATURES

Recently, a novel fusion in this variant of iCCA involving the exon 8 of *NIPBL* and exon 2 of *NACC1, NIPBL::NACC1* has been identified in 3 cases[7]. An additional case was identified by the authors in the Cancer Genome Atlas harboring an identical fusion (case TCGA-ZH-A8Y6). The digital slide of this case available online (www.cbioportal.org) shows the characteristic morphologic features of solid-tubulocystic variant of iCCA. Most recently, a subsequent study reported one case to harbor this fusion[5]; hence to date 5 cases have been identified with this novel fusion. However, it remains unclear if this fusion is specific for this tumor type. To date this exact fusion has only been reported in 2 other malignancies both reported as "noncolorectal and nonpancreas gastrointestinal primary[15]." Unfortunately, no

**Table 1 Aggregated selected immunophenotype[5,6,7,8,11], *n* (%)**

| Antibody | Positive | Negative |
|---|---|---|
| Inhibin | 14 (100) | 0 |
| Cytokeratin AE1/AE3 | 6 (100) | 0 |
| CAM5.2 | 4 (100) | 0 |
| Cytokeratin-7 | 14 (100) | 0 |
| Cytokeratin-19 | 12 (100) | 0 |
| Cytokeratin-20 | 0 | 6 (100) |
| CDX2 | 0 | 3 (100) |
| Arginase-1 | 0 | 5 (100) |
| HepPar1 | 0 | 13 (100) |
| Glypican-3 | 1 (12.5) | 7 (87.5) |
| Glutamine synthetase | 3 (100) | 0 |
| Albumin by *in situ* hybridization | 6 (100) | 0 |
| Synaptophysin | 10 (76.9) | 3 (23.1) |
| Chromogranin | 9 (64.3) | 5 (35.7) |
| CD56 | 5 (71.4) | 2 (28.6) |
| INSM1 | 4 (100) | 0 |
| Beta-catenin | 0 | 7 (100) |
| CD10 | 0 | 3 (100) |
| Pax8 | 0 | 2 (100) |
| Gata3 | 0 | 1 (100) |
| Mammaglobin | 0 | 1 (100) |
| GCDFP-15 | 0 | 1 (100) |
| ER | 0 | 2 (100) |
| PR | 0 | 2 (100) |
| S100 | 0 | 3 (100) |

CDX2: Caudal-related homeobox gene 2; INSM1: Insulinoma associated protein 1; GCDFP-15: Gross cystic disease fluid protein 15; ER: Estrogen receptor; PR: Progesterone receptor; HMB45: Human melanoma black 45; pCEA: Polyclonal carcinoembryonic antigen; mCEA: Monoclonal carcinoembryonic antigen; SF-1: Steroidogenic factor 1; WT-1: Wilms tumor 1; TTF-1: Thyroid transcription factor 1; AFP: Alpha fetoprotein; CA125: Cancer antigen 125; CA19.9: Cancer antigen 19.9; SALL4: Sal-like 4; Oct3/4: Octamer binding transcription factor 3/4; PLAP: Placental-like alkaline phosphatase; hCG: Human chorionic gonadotrophin; RCC: Renal cell carcinoma; SOX9: SRY-box transcription factor 9.

description of the morphology of these two tumors is available. Although this fusion appears to be specific for this tumor at this time, given its characteristic morphology and immunohistochemical profile, molecular testing may not be necessarily needed in our opinion for diagnostic purposes.

The *NIPBL* (Nipped-b homolog) gene codes the protein delangin[16], a cohesin loading factor, which is essential for the chromatin loading of cohesin, an important ring-shaped protein complex for the structural organization of chromosomes and for the repair of DNA double-strand breaks[17]. Delangin also plays a role in translocating cohesin along the chromatin fibers which is thought to be the underlying pathogenesis of Cornelia de Lange syndrome[18,19]. Additionally, *NIPBL* plays a crucial role in myeloid differentiation[20]. Loss-of-function of *NIPBL* has been associated with an increased number of myeloid progenitors and a decrease of mature myeloid cells, and has been reported in acute megakaryoblastic leukemia[21,22]. In solid tumors, variant in *NIPBL* occurs in tenosynovial giant cell tumor, specifically a *NIPBL::ERG* fusion[23]. Interestingly, NIPBL overexpression has been shown to correlate with poor prognosis and chemotherapy resistance in non–small cell lung cancer, and knockdown of NIPBL in non–small cell lung cancer cell or breast cancer cell lines induces impaired proliferation, cell cycle arrest, apoptosis and autophagy[24-26]. NAC1 coded by *NACC1* is a member of the Bric-a-Brac Tramtrack Broad (BRB) family of protein complex which is also known as pox virus and zinc finger (POZ). This protein complex has multiple cellular functions involving in cellular proliferation, apoptosis, protein degradation, transcription and cellular morphology, among others[27-29]. NAC1 is associated with development of endometrial carcinomas[29], and tumor recurrence[28], and the development of chemoresistance in ovarian cancers[30-

32]. Although both *NIPBL* and *NAC1* genes have a crucial role in cellular proliferation and DNA repair, it is unclear to date what is the mechanistic function of their fusion protein. Future studies are needed to understand its biological function of this fusion which could lead potentially to the development of targeted therapies.

## DIFFERENTIAL DIAGNOSIS

Metastatic or primary hepatic WD-NETs often share similar histologic pattern, cytologic morphology and positivity of neuroendocrine markers as this solid-tubulocystic variant of iCCA. One of the main clues for a solid-tubulocystic variant of iCCA is the multiple growth patterns present within each case in contrast to WD-NET which tends to have a more homogenous growth pattern. However, immunohistochemistry work-up is essential in their distinction. Although both WD-NET and solid-tubulocystic variant of iCCA can express neuroendocrine markers (synaptophysin and chromogranin), the expression of CK7 and CK19, and albumin by in-situ hybridization in solid-tubulocystic variant of iCCA rules out a diagnosis of WD-NET. Since the morphologic similarity with metastatic ACC, a possibility of ACC needs to be excluded. The negative expression of neuroendocrine markers (synaptophysin and chromogranin) and the positive expression of acinar markers (BCL10, trypsin and chymotrypsin) can help to rule out solid-tubulocystic variant of iCCA. Of note, about 25% of the pancreatic ACCs are positive for albumin by in-situ hybridization[33]. The cystic and glandular architecture containing colloid-like secretions is reminiscent of thyroid follicular neoplasm. The negative expression of TTF-1 or thyroglobulin can help to exclude the possibility of metastatic follicular neoplasm. Although uncommon, a metastatic sex-cord stromal tumor may enter the differential diagnosis given the expression of inhibin and similarity of some of the morphologic features. However, the expression of CK7, CK19, neuroendocrine markers and albumin by in-situ hybridization by solid-tubulocystic variant of iCCA can help to rule out this possibility.

## TREATMENT CONSIDERATIONS

Given the rarity of these cases it remains unclear what is the optimal management plan for patients with this new variant iCCA. The majority of the cases reported with available information underwent a complete surgical resection ranging from segmentectomies to lobectomies, and one case was deemed not a surgical candidate given the presence of widely metastatic disease[5-9]. Two patients were treated before resection, one with neoadjuvant chemotherapy and one with transarterial chemoembolization[6]. The non-surgical candidate was treated with cisplatin and gemcitabine[9]. Most of the patients were treated with adjuvant chemotherapy after resection with a similar regimen, cisplatin and gemcitabine [7]. The previously reported pediatric patient was treated with a different regimen which included capecitabine[5].

## CONCLUSION

Inhibin-positive hepatic carcinoma with solid-tubulocystic features (solid-tubulocystic carcinoma) is a recently recognized iCCA variant which predominantly presents in young woman with a large size at presentation. They have a characteristic morphology of round to oval cells with scant to moderate amount of eosinophilic cytoplasm which are organized in multiple different growth patterns including solid, tubular, and cystic. This novel variant is associated with a characteristic fusion gene, *NIPBL::NAC1*, being the first iCCA with a described recurrent gene fusion. Although much remains unknown of this variant based on the reported cases to date, they are associated with relatively favorable outcome with a 25% mortality rate compared to the 7%-20% 5-year survival rate of typical iCCAs[2]. Further studies are needed to fully explore the biological function of this fusion gene and its role in the tumorigenesis and to continue to characterize this rare tumor.

## FOOTNOTES

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