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**RESEARCH ARTICLE**

# DIAGNOSTIC DILEMMA: INTRACHOLECYSTIC NEOPLASM OF THE GALLBLADDER MIMICKING MALIGNANCYIN A TERTIARY CARE CENTRE IN TAMIL NADU

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## ABSTRACT

A 65-year-old female presented to a tertiary care hospital in a western district of Tamil Nadu with complaints of right upper quadrant abdominal pain and reduced appetite for the past 3 days. CECT abdomen revealed cholelithiasis with a thickened gall bladder wall, along with a lesion arising from the fundus and projecting into the lumen, which is suspicious of malignancy. The patient has been taken for a laparoscopic cholecystectomy. Grossly, the gall bladder showed a thickened wall with an exophytic growth with the papillary projections in the fundus. Microscopically, after thorough analysis of the specimen, it has been concluded as a low-grade intracholecystic papillary neoplasm of Gall bladder-biliary type. Immunohistochemical studies have also been performed to confirm the diagnosis, which showed positivity for EMA (MUC1) and CK7. In this case report, we discuss the clinicopathologic perspective of this distinct entity and evidence that ICPN may mimic carcinoma radiologically and macroscopically. Thus, a thorough histopathological examination is necessary for the diagnosis of ICPN, which exhibits a good prognosis.



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# INTRODUCTION

Intracholecystic papillary neoplasm (ICPN) of the gall bladder is a rare, distinct entity that was first identified in 2010. Later in 2019, due to its progressive nature, ICPN was recognized as a preinvasive lesion of the gall bladder in the World Health Organization (WHO) classification of tumors of the digestive system.[1] Now, in the 6th edition of the WHO classification of digestive tumors, mass-forming lesions of the gall bladder have been recognized as intracholecystic neoplasm and further subdivided into Intracholecystic papillary neoplasm and Intracholecystic tubular neoplasm.[2] Based on the literature. ICPN has been reported in 0.4% of all cholecystectomies, and 6% of gall bladder carcinoma arises from the ICPN.[1,3] Though a considerable number of literatures were available on the ICPN of the gall bladder, only a few cases have been reported in Tamil Nadu. This case report describes the clinical presentation and histomorphological features of ICPN of the gallbladder in a 65-year-old female from our region.

# CASE REPORT

A 65-year-old female presented to a tertiary care hospital with complaints of right upper quadrant abdominal pain and decreased appetite. Ultrasound of the abdomen showed echogenic foci with gallstones and a thickened gallbladder. An abdominal and pelvic CT with intravenous contrast detected cholelithiasis and also demonstrated an irregular, thickened gallbladder wall measuring 9mm along with a 39 x 28 mm-sized heterogeneous lesion in the fundal region projecting into the lumen with post-contrast enhancement.In view of clinical symptoms and malignancy suspicion, Laparoscopic Cholecystectomy was done, and intraoperatively, the gall bladder wall was thickened. On gross examination, the gall bladder measured 8x3x2cm and the cut section showed a thickened wall measuring 0.8cm, and the fundus showed an exophytic growth with papillary projections projecting into the lumen (Fig. 1). Microscopically, sections studied from the growth showed a neoplasm arising from the gall bladder

mucosa, arranged in papillary configuration. The papillae are lined by a single layer of cuboidal cells having scant to moderate eosinophilic cytoplasm and hyperchromatic nuclei exhibiting mild pleomorphism. Underlying lamina propria and muscularis layers are free of tumor. Then the specimen was entirely processed to look for invasion, and confirmed that there is no invasion. Adjacent areas show extensive mucosal ulceration. Hence, it was diagnosed to be a low-grade intracholecystic papillary neoplasm of biliary type (Figure 2).

Immunohistochemical studies have been performed to confirm the morphological pattern of ICPN. Figures 5 and 6 showed diffuse positivity for CK7 and Apical positivity for EMA, which confirms the biliary pattern of ICPN. She has been under regular follow-up, and the recent post-op CT scan performed 3 months after surgery showed no significant lesions.

**Figure 1. Cut section of Gall bladder specimen showing exophytic growth with papillary projections.**

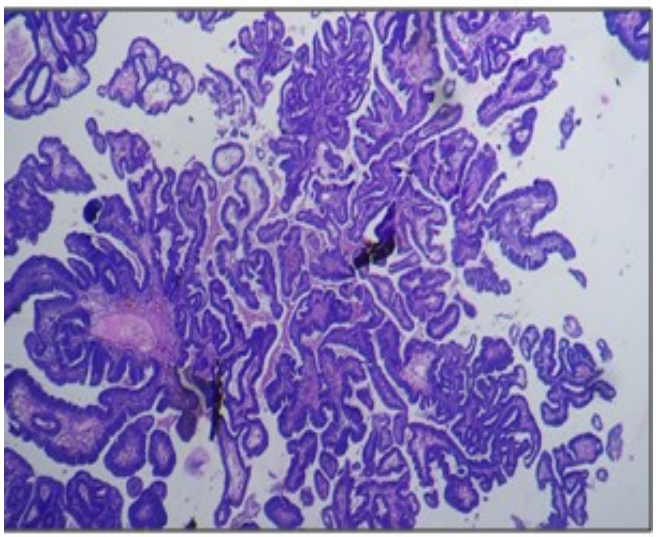

**Figure 2. Microscopically, ICPN of gall bladder arranged in papillary pattern(H&E stain, 100x)**

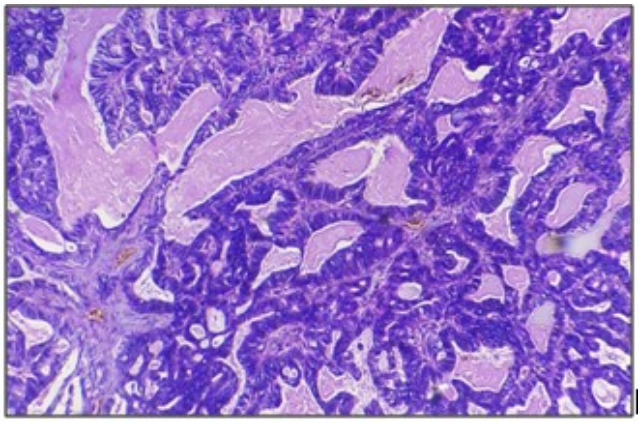

**Figure 3. ICPN of gall bladder showing low grade dysplasia (H&E stain, 400x)**

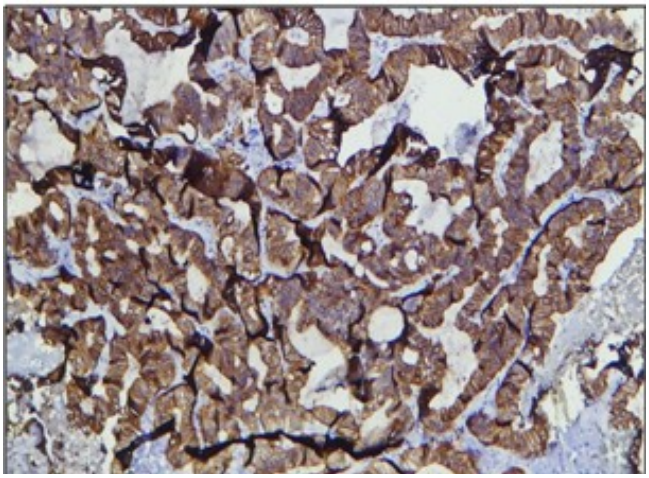

**Figure 4. Immunohistochemical staining showing diffuse positivity for CK 7**

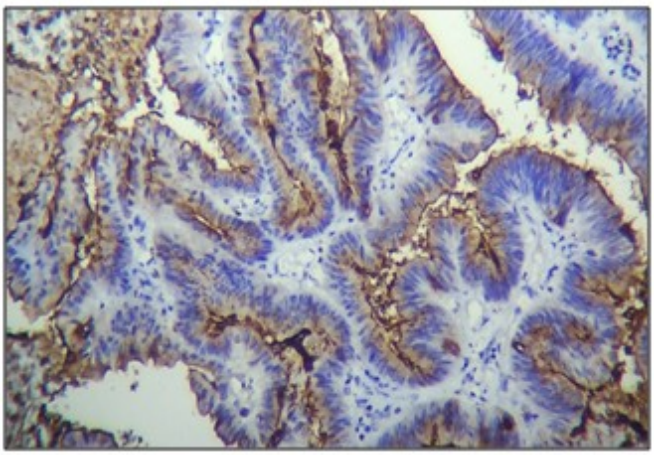

**Figure 5. Immunohistochemical staining showing apical positivity for EMA**

# DISCUSSION

Intracholecystic papillary neoplasm of the gall bladder is a rare entity with an incidence of 0.4% of cholecystectomies.[1,3] ICPN has been recognised as a preinvasive neoplasm of the gall bladder by the WHO in 2019. Recently, in the WHO 6th edition of classification of tumours of the digestive system, mass-forming precursor lesions in the gall bladder are named as intracholecystic neoplasm and are subdivided into intracholecystic papillary neoplasm and intracholecystic

**Table 1: Morphological patterns recognised in ICN of gall bladder**

| Morphological pattern | Microscopic features | Immunohistochemistry |
|---|---|---|
| Biliary type | Most common Glands lined by cuboidal epithelium with clear to eosinophilic cytoplasm, Enlarged nuclei with prominent nucleoli | Positive for CK7 and EMA (MUC 1) |
| Gastric type (Gastric foveolar type) | Elongated glands lined by tall columnar epithelium with abundant pale cytoplasm and peripherally located nuclei | Diffusely positive for MUC5AC, MUC6 |
| Intestinal type | Glands are lined by tall columnar epithelium with basophilic cytoplasm and pseudostratified cigar shaped nuclei | Positive for CK20, CDX2, MUC2 |
| Oncocytic morphology | Less common Arboring papillae lined by multilayered cells with abundant granular acidophilic cytoplasm and single prominent nucleoli. | Positive for EMA |

tubular neoplasm, similar to biliary duct lesions.[2] Like Intraductal papillary mucinous neoplasm(IPMN), Intraductal papillary neoplasm of the bile duct, ICPN of gall bladder also follows adenoma carcinoma sequence involving mutations in STK11, CTNNB1 and APC. In contrast, p53 mutations are commonly seen in polypoidal cancers of the gall bladder.[1,3,4] Intracholecystic neoplasm of the gall bladder may occur in a wide range of age distribution from 49 to 94 yrs with female predilection. Though a few cases had also been reported in young females around 23 yrs.[4] As the age advances, the risk of invasion increases.[1] ICPN is often diagnosed incidentally, and some patients present with abdominal pain, jaundice and weight loss.[4-6] Our patient is a 65-year-old female who presented with right upper quadrant abdominal pain. Many patients diagnosed with ICPN of the gall bladder were diabetic and hypertensive, although the association between them is not clearly understood. Lab investigations of some patients revealed neutrophilic leucocytosis, which indicates the underlying acute inflammatory pathology.[6,7] Most of the ICPN cases were associated with cholelithiasis, which supports the evidence of cholelithiasis in our study.[8,9] ICPN of the gall bladder can also arise in patients with hepatic disorders.[10] In contrast-enhanced CT scan, ICPN of the gall bladder can be identified as a polypoidal growth and thickened mass, which raises suspicion of malignancy.[6,7]However, Imaging modalities in some studies revealed gall bladder wall thickening alone. ICPN lesions have been misinterpreted as sludge or debris in a few studies.[5,10] In this study, a CT scan revealed exophytic growth with papillary projections in the lumen. Most cases of ICPN are treated with Laparoscopic cholecystectomy, similar to our case, and a few with radical cholecystectomy.[4,7]

Grossly, ICPN presents as a visible, mass-forming lesion in the lumen of the gall bladder.[1] It can also present as an ulcero-proliferative lesion, which mimics malignancy.[9] Microscopically, ICPN has 4 subtypes – Gastric, biliary, intestinal and oncocytic based on the histomorphological and immunohistochemical findings (Table 1). If >75% of neoplasms are of one subtype, the lesion is described as mono-subtype, and if two or more subtypes are noted, then it is labelled as mixed subtype.[1,3] While gastric and biliary subtypes are commonly encountered, ICPN with a biliary subtype has an increased risk of association with invasive adenocarcinoma.[12,3] ICN also arise from the adenomyomatous nodule in the gall bladder.[8] Based on the cytomorphological features, ICPN can be graded using 2 tier grading system as low grade and high grade.[3] Studies have revealed that adenocarcinoma of the gall bladder has an association with ICPN, and ICPN with high grade were associated with biliary intraepithelial lesion of low grade and high grade, but low grade ICPN can be associated with low grade biliary intraepithelial neoplasia or even with no dysplasia. However, ICPN of low grade were not associated with higher grade lesions.[3] These ICPNs may progress to conventional nodular sclerosing gallbladder carcinoma of the gallbladder wall with variably-sized visible intraluminal papillary lesions. Studies also revealed that ICPNs involving Rokitansky Aschoff sinuses were associated with aggressive behaviour.[1,8]We conclude that, although considerable cases of ICPN of the gall bladder have been reported worldwide, limited cases were published in a Tamil Nadu to our knowledge. Hence, considering the rarity of the case, we reinforce that the clinicians and pathologists should be aware of the preinvasive nature of ICPN. So, before diagnosing ICPN of the gall bladder, the need for complete processing of the specimen plays a crucial role, which carries better than ICPN with invasive adenocarcinoma component.

**Conflict of Interest:** The authors declare no conflicts of interest.

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**Ethical approval:** Ethical approval for this case report was waived by the Institutional Ethics Committee in accordance with our institutional policy for retrospective case reports; however, the study was conducted in strict adherence to the ethical principles of the Declaration of Helsinki.

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