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THE RELATIONSHIP BETWEEN INTRACHOLECYSTIC PAPILLARY-TUBULAR NEOPLASMS AND INVASIVE CARCINOMA OF THE GALLBLADDER: A PATHOLOGY CASE SERIES

Pathology

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ABSTRACT

Intracholecystic papillary-tubular neoplasms (ICPNs) are mass-forming, ≥1 cm, intramucosal preinvasive neoplasms of the gallbladder that show variable papillary and tubular architecture and distinct cell lineages, with heterogeneous risk of associated invasive carcinoma[1]. The proliferative marker Ki-67 has been proposed as a significant factor correlating with the likelihood of invasion in ICPN[2]. This case series describes several gallbladder ICPNs identified in routine cholecystectomy specimens at a single tertiary center, emphasizing their architectural and lineage subtypes, the presence and extent of high-grade dysplasia, associated invasive carcinoma, and Ki-67 labeling indices where available. The series illustrates that lesions with papillary or tubulopapillary configuration, biliary or gastric-foveolar lineage, diffuse high-grade dysplasia, and high Ki-67 index are most often associated with early invasive adenocarcinoma, whereas pyloric-type and purely inflammatory cases show low Ki-67 indices and no invasion[1][2]. Recognition and standardized reporting of ICPN, including Ki-67 assessment, may improve risk stratification and guide clinical management.

KEYWORDS

INTRODUCTION

ICPN was proposed as a unified term for exophytic, intramucosal, preinvasive gallbladder neoplasms measuring at least 1 cm, encompassing lesions previously labeled as adenomas, papillary neoplasms and intracystic papillary neoplasms[1][3]. These tumors exhibit biliary, gastric pyloric, gastric foveolar, intestinal or oncocytic lineages and show a spectrum from low-grade to high-grade dysplasia, frequently coexisting within the same lesion[1][3]. Approximately 55% of ICPNs in large series harbor an associated invasive carcinoma, but their overall prognosis—particularly when invasion is limited—is significantly better than that of conventional pancreatobiliary-type gallbladder adenocarcinoma unassociated with ICPN[1][2].

Ki-67 labeling index reflects cellular proliferative activity and has been correlated with invasion in ICPN: cases with invasive carcinoma show significantly higher Ki-67 indices (mean ~33%) than non-invasive lesions (mean ~12%)[2]. Architectural pattern (papillary/tubulopapillary vs. tubular), extent of high-grade dysplasia, and biliary or foveolar lineage have also been linked to higher risk of invasion[1][2][3]. The present case series applies the ICPN framework and Ki-67 assessment to a small group of cholecystectomy specimens to highlight practical reporting points and clinicopathologic correlations.

Case Descriptions

Case 1: Chronic cholecystitis with granulomatous inflammation (non-ICPN comparator) Clinical presentation and gross findings:

A 52-year-old woman presented with right upper quadrant pain and was found on ultrasound to have gallstones. Cholecystectomy was performed for symptomatic cholelithiasis. The gross specimen consisted of an intact gallbladder without a discrete exophytic mass; the wall showed focal thickening and multiple calculi of varying sizes.

Microscopic findings:

Histology demonstrated acute necrotizing and chronic cholecystitis with cholelithiasis and focal granulomatous inflammation. No compact intramucosal polypoid lesion ≥1 cm was identified, and the epithelium did not show dysplastic changes. The cystic duct margin was free of dysplasia. The attached hepatic tissue showed only mild chronic inflammatory changes.

Pathologic interpretation:

This case does not meet criteria for ICPN diagnosis, which requires a well-demarcated, mass-forming dysplastic proliferation distinct from diffuse reactive changes [4,5]. It serves as an important inflammatory background comparator, emphasizing that chronic cholecystitis and cholelithiasis alone—even with prominent inflammation—do not constitute ICPN unless there is a discrete ≥1 cm intramucosal proliferative lesion with epithelial dysplasia.[5]

Case 2: ICPN with papillary-tubulopapillary architecture, extensive high-grade dysplasia, and early invasive carcinoma with elevated Ki-67 Clinical presentation and gross findings:

A 74-year-old man underwent laparoscopic cholecystectomy for suspected chronic calculous cholecystitis. At surgery, a polypoid mass was appreciated within the gallbladder lumen. Grossly, the gallbladder contained a friable, gray-white exophytic mass measuring approximately 8.5 × 2 × 1 cm arising from the body-fundus region. The gallbladder lumen was free of stones. The surrounding wall showed areas of thickening consistent with chronic inflammation.

Microscopic findings:

Multiple sections revealed a compact intraluminal proliferation of papillary and tubulopapillary fronds. The lesion was composed predominantly of biliary-type and gastric-foveolar-type epithelium with extensive high-grade dysplasia affecting more than 75% of the lesion[1]. The diagnostic criteria for ICPN were fully met, including size ≥1 cm, intramucosal location, and distinct compact architecture separate from the adjacent mucosa. Small foci of early invasive adenocarcinoma infiltrating the lamina propria and superficial muscular layer (pT1) were present at the base of the ICPN, consistent with "ICPN with associated early invasive carcinoma." Lymphovascular invasion was not identified.

Immunohistochemical findings:

Immunohistochemistry was performed with cell lineage markers including CK7, CK20, MUC1, MUC2, and MUC5AC to confirm biliary and gastric differentiation. Ki-67 proliferation index was markedly elevated, consistent with published data showing that invasive ICPNs demonstrate significantly higher Ki-67 indices than non-invasive lesions[6-8].

Pathologic interpretation:

This case exemplifies an ICPN with high-risk features: papillary and tubulopapillary architecture, extensive high-grade dysplasia, and early invasive adenocarcinoma. The elevated Ki-67 index supports the documented association between high proliferative activity and invasive potential [9]. The presence of early stromal invasion represents approximately 55% of ICPN cases where invasion is detected [1].

Case 3: ICPN with high-grade intraepithelial neoplasia and focal early invasion Clinical presentation and gross findings:

A 68-year-old woman underwent partial cholecystectomy for a suspicious polypoid gallbladder lesion discovered during surgical exploration for acute cholecystitis. The submitted specimen consisted of a partially opened gallbladder wall fragment with an irregular gray-brown mucosal lesion measuring 5 × 2 × 2 cm associated with loss of the normal velvety mucosa. The adjacent gallbladder wall showed signs of acute and chronic inflammation.

Microscopic findings:
Histologic examination revealed a well-circumscribed intramucosal papillary and tubulopapillary proliferation fulfilling diagnostic criteria for ICPN[1]. The lesion was composed mainly of epithelium with high-grade intraepithelial neoplasia, with areas of low-grade dysplasia identifiable at the lesion periphery—a common finding representing the adenoma-carcinoma sequence[10]. Small foci of early invasive adenocarcinoma limited to the lamina propria and superficial muscularis propria were present, indicating pT1 invasion. The adjacent hepatic tissue showed only mild chronic inflammation without evidence of widespread invasion.

Immunohistochemical findings:
Immunohistochemical work-up with CK7, CK20, CDX2, MUC1, MUC2 and Ki-67 was recommended to fully subtype the lesion (likely biliary or gastric-foveolar lineage) and quantify proliferative activity. Based on the morphology of extensive high-grade dysplasia with associated invasion, Ki-67 would be expected to be elevated, consistent with series data showing high Ki-67 in invasive lesions[11].

Pathologic interpretation:
This case illustrates an ICPN with the full spectrum of dysplasia from low-grade to high-grade and with definite—albeit early—stromal invasion. The presence of a transition zone from low-grade dysplasia to high-grade dysplasia supports the concept of an adenoma-carcinoma sequence within ICPN[1]. Early detection and complete specimen sampling have clinical importance, as stage-matched comparisons show better outcomes for ICPN-associated carcinomas versus conventional pancreatobiliary-type adenocarcinoma[12].

Case 4: ICPN with tubular-tubulopapillary architecture, focal high-grade dysplasia, no definite invasion, and lower Ki-67 Clinical presentation and gross findings:
A 44-year-old man underwent cholecystectomy for symptomatic gallstones and a radiologically detected gallbladder polyp. Grossly, the 10 cm gallbladder contained a polypoid intraluminal lesion with blackish stone material adhered to its surface and velvety mucosal changes with variable wall thickening ranging from 0.2 to 0.4 cm. The specimen appeared otherwise unremarkable except for features of chronic cholecystitis.

Microscopic findings:
Microscopic examination revealed an intraluminal proliferation that met size and architectural criteria for ICPN. The predominant pattern was tubular and tubulopapillary, composed primarily of pyloric-type and gastric-type glands with dense back-to-back architecture and minimal intervening stroma. Focal segments displayed high-grade dysplasia, but no unequivocal stromal invasion was identified in the submitted sections[13]. The base of the lesion was sharply demarcated from the underlying muscularis, supporting the intramucosal classification. The surrounding gallbladder wall showed chronic cholecystitis with cholelithiasis.

Immunohistochemical findings:
Immunohistochemistry with CK7, CK20, MUC1, MUC2, CDX2, TP53 and KRAS was recommended by the pathologists to further subtype the lesion and rule out occult invasion. Ki-67 was expected to be lower than in frankly invasive ICPN, consistent with published data demonstrating significantly lower Ki-67 indices in non-invasive cases (mean ~12%) compared with invasive lesions (mean ~33%)[2,11,14].

Pathologic interpretation:
This case represents ICPN with predominantly low-to-intermediate-grade features and focal high-grade dysplasia but no definite invasion. The pyloric/gastric-type lineage and tubular architecture are associated with lower rates of high-grade dysplasia and invasion compared with biliary-predominant and papillary-predominant lesions[1,3,15]. The focal nature of high-grade dysplasia in an otherwise low-grade lesion suggests that complete histologic sampling may be critical to exclude small foci of invasion, and the recommended Ki-67 and molecular studies would provide additional risk stratification[2,16].

Case 5: Low-grade biliary epithelial proliferation with chronic cholecystitis and minimal Ki-67 Clinical presentation and gross findings:
A 49-year-old woman underwent cholecystectomy for symptomatic cholelithiasis and chronic biliary symptoms. Grossly, the gallbladder showed chronic inflammation with multiple stones and no large exophytic mass. The mucosal surface appeared irregular but without a focal polypoid lesion ≥1 cm.

Microscopic findings:
Microscopic examination revealed chronic cholecystitis with cholelithiasis and focal areas of low-grade biliary epithelial proliferation. While some areas resembled low-grade features of intraepithelial neoplasia, no compact ≥1 cm intramucosal mass was identified, and dysplasia was not prominent[1,17]. The lesion does not fully meet diagnostic criteria for ICPN in its classic sense, but illustrates the spectrum of low-grade proliferative change that can occur in chronically inflamed gallbladders. The epithelium showed regular architecture with only minimal cytologic atypia.

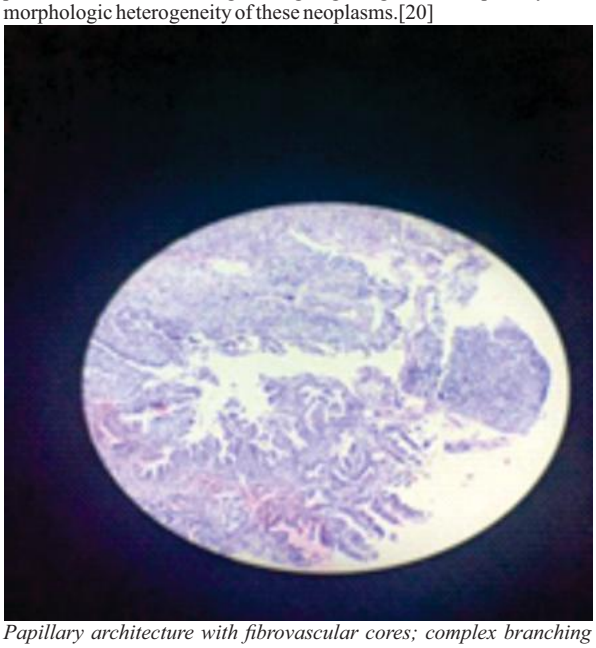
Immunohistochemical findings:
Immunohistochemistry on the excised gallbladder demonstrated CK7 negativity in the tested focus, MUC1 with weak staining, and a low Ki-67 labeling index (<5%), with wild-type p53 pattern. These findings favor a non-neoplastic or very early, minimally dysplastic neoplastic process rather than established ICPN[3,18].

Pathologic interpretation:
This case illustrates those low-grade biliary epithelial proliferations with minimal cytologic atypia and low Ki-67 labeling show negligible risk of progression to invasive carcinoma. This is concordant with the literature demonstrating that lesions lacking a clearly defined ≥1 cm compact mass and showing only low-grade changes are usually clinically inconsequential and warrant conservative follow-up rather than aggressive intervention [1,3,19]. The case serves as an important comparator showing the natural history of chronic cholecystitis without true ICPN.

DISCUSSION

Definition and Diagnostic Criteria of ICPN
ICPNs are defined as intramucosal, exophytic, papillary or polypoid gallbladder masses ≥1.0 cm composed of dysplastic epithelium forming a compact lesion that is distinct from the adjacent mucosal epithelium[1]. This diagnostic threshold of 1.0 cm parallels the criteria used to distinguish tumoral intraepithelial neoplasms from non-tumoral dysplasias in other pancreatobiliary organs, including intraductal papillary mucinous neoplasms and intraductal tubulopapillary neoplasms of the pancreas and intraductal papillary neoplasms of the bile ducts[1][3]. Lesions smaller than 1.0 cm, even if dysplastic, are considered incipient forms or polypoid hyperplasia and are managed conservatively unless symptomatic[3].

The unification of terminology under the heading of ICPN was proposed to resolve longstanding confusion in the literature, where these lesions had been referred to variously as pyloric gland adenomas, papillary adenomas, papillary carcinomas, biliary adenomas, intestinal adenomas and intracystic papillary neoplasms—terms that were often based on growth pattern, cell lineage or degree of dysplasia without clear consensus on definitions[1]. The ICPN framework acknowledges that a single lesion frequently displays multiple growth patterns and cell lineages, highlighting the complexity and morphologic heterogeneity of these neoplasms.[20]



Papillary architecture with fibrovascular cores; complex branching papillae lined by dysplastic biliary epithelium.

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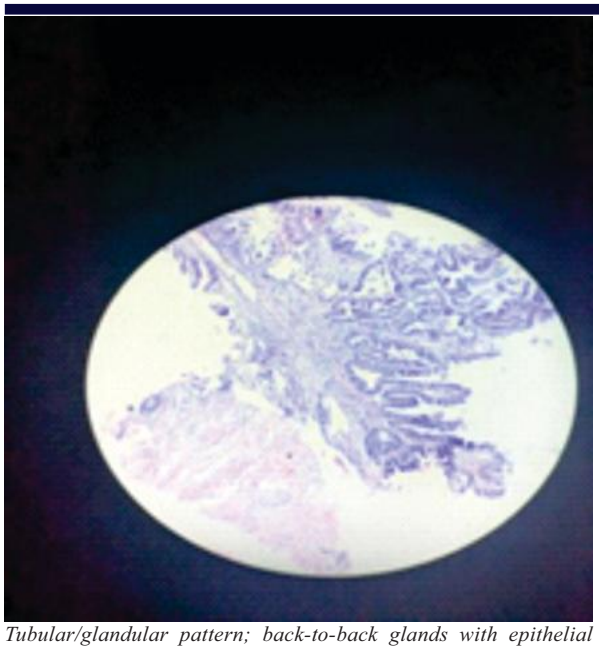
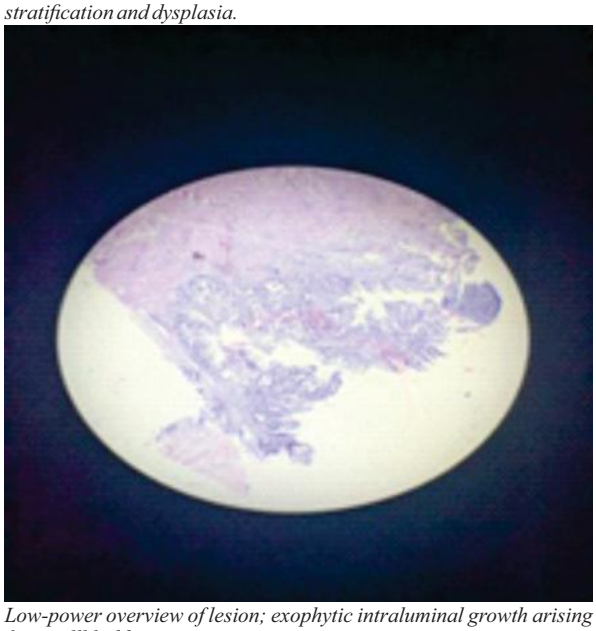
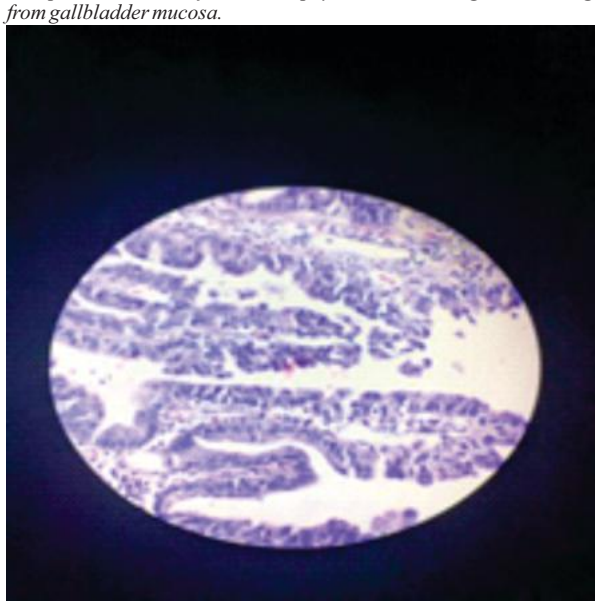


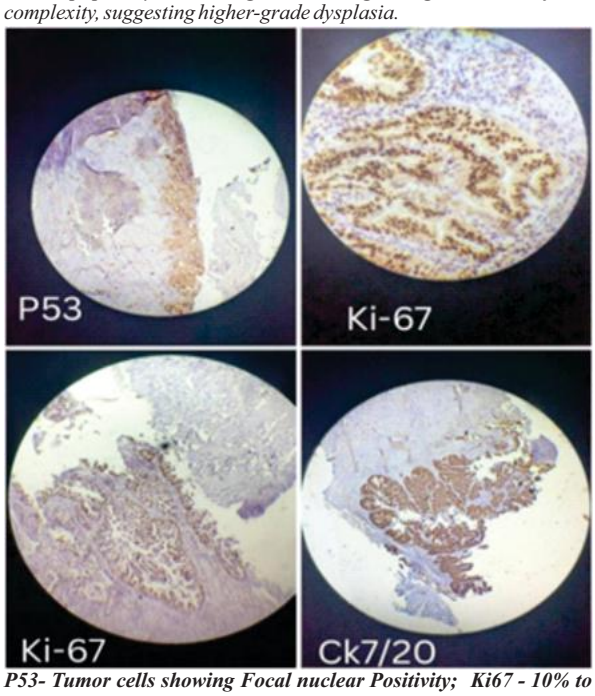
Tubular/glandular pattern; back-to-back glands with epithelial stratification and dysplasia.



Low-power overview of lesion; exophytic intraluminal growth arising from gallbladder mucosa.



Mixed papillary–tubular growth; irregular glands with focal complexity, suggesting higher-grade dysplasia.



P53- Tumor cells showing Focal nuclear Positivity; Ki67 - 10% to 40% of the tumor cells show Positivity; Ck7/20 - Tumor cells showing Focal nuclear Positivity.

Figure 2: Immunohistochemical of Intracholecystic Papillary-Tubular Neoplasm

Histologic Spectrum and Cell Lineage Classification

ICPNs display a broad histologic spectrum encompassing three predominant growth patterns: papillary (>75% papillary/villous growth), tubular (>75% tubular gland formation), and tubulopapillary (mixed pattern with 25-75% of either component)[1]. Our case series demonstrates all three patterns. The papillary and tubulopapillary lesions (Cases 2 and 3) showed higher-grade dysplasia and invasive potential, whereas the predominantly tubular lesion (Case 4) had lower-grade features and no invasive carcinoma, consistent with published observations[21].

Regarding cell lineage, ICPNs commonly show five phenotypes based on morphology and immunohistochemical profile[1,3]:

1. Biliary phenotype (~50-70% of cases): characterized by simple to pseudostratified cuboidal cells resembling normal gallbladder epithelium, with CK7 and MUC1 positivity. Biliary-predominant lesions are frequently associated with papillary architecture and high-grade dysplasia[1].

2. Gastric pyloric subtype (~17-20% of cases): composed of compact, small, uniform pyloric glands with low nuclear-cytoplasmic ratios, diffuse MUC6 positivity, and commonly low-grade dysplasia. These lesions carry the lowest risk of invasive carcinoma (~6%)[1,3].

3. Gastric foveolar subtype (~2-16% of cases): characterized by elongated glands lined by tall columnar cells with abundant pale cytoplasm and peripherally located nuclei. MUC5AC positivity is present in 100% of cases. This subtype is frequently associated with high-grade dysplasia (~95%) and intermediate risk of invasion[1,3].

4. Intestinal subtype (~8-14% of cases): resembles colonic adenomas with pseudostratified, basophilic, crowded nuclei ("cigar-shaped"). MUC2 and CDX2 positivity is characteristic. Invasion risk is intermediate[1,3].

5. Oncocytic subtype (~6% of cases): rare, composed of oncocytic cells with prominent mitochondria, CK7 and MUC1 positivity. This represents the least common phenotype[1,3].

In our series, Cases 2 and 3 featured biliary and mixed biliary-foveolar lineage with high-grade dysplasia and invasion, while Case 4 showed

predominantly gastric-pyloric features with lower-grade dysplasia and no invasion. These observations align with published data showing that biliary and foveolar lineages carry higher invasive potential than pure pyloric-type lesions[17].

Relationship to Invasive Carcinoma

The association between ICPN and invasive adenocarcinoma is well-documented. In large series analyzing 123 ICPNs, approximately 55% contained an associated invasive carcinoma component, and ICPN-associated carcinomas accounted for 6.4% of all gallbladder adenocarcinomas[1]. Importantly, when invasion is identified, the invasive component is typically located at the base of the polyp (72% of cases) but can occasionally arise in the polyp head or at separate sites[1].

Several morphologic features have been found to correlate significantly with invasive potential:

Papillary or tubulopapillary architecture: All ICPN cases with invasive carcinoma in one series showed papillary or tubulopapillary growth patterns, whereas purely tubular lesions rarely harbored invasion[2].

Extent of high-grade dysplasia: Lesions with extensive (>75%) high-grade dysplasia showed invasive carcinoma in 71% of cases, compared with only 31% of lesions with focal high-grade dysplasia[1].

Biliary or foveolar lineage: Biliary-predominant ICPNs showed invasive carcinoma in 69% of cases, versus 6% for pyloric-predominant lesions[1].

Lesion size: The median size of lesions with invasion was 4.39 cm, compared with 2.76 cm for non-invasive lesions, suggesting that larger size correlates with higher risk[2].

Cases 2 and 3 in our series exemplify the high-risk phenotype: both displayed papillary/tubulopapillary architecture, high-grade dysplasia, and biliary or mixed lineage—features predictive of invasion. Case 4, with its predominantly tubular-pyloric architecture and focal dysplasia, represents a lower-risk category and indeed showed no definite invasion.

A critical clinical point is that even when invasion is present in ICPN, the prognosis is substantially better than that of conventional pancreatobiliary-type gallbladder adenocarcinoma. Three-year actuarial survival for non-invasive ICPN is approximately 90%, decreasing to 60% for ICPN-associated invasive carcinoma[1]. In striking contrast, pancreatobiliary-type gallbladder carcinomas unassociated with ICPN have a 3-year survival of only 27%[1]. This prognostic advantage underscores the importance of recognizing and reporting ICPN separately from conventional adenocarcinoma.

Ki-67 Proliferation Index as a Predictive Marker

Ki-67 is a nuclear antigen expressed during all active phases of the cell cycle (G1, S, G2, and M) but absent in G0 (resting phase), making it a useful marker of cellular proliferation[2]. In a focused analysis of 45 ICPN cases, a statistically significant correlation was demonstrated between Ki-67 labeling index and the presence of invasive carcinoma ($p = 0.0001$)[18].

Specifically, ICPN cases with invasive carcinoma showed a mean Ki-67 index of 32.75 ± 18.88%, whereas non-invasive cases had a mean Ki-67 index of 11.68 ± 15.82%—a threefold difference[2]. Furthermore, high Ki-67 index was associated with diffuse high-grade dysplasia and papillary or tubulopapillary growth patterns, features already recognized as risk factors for invasion[18].

The practical implication is that quantifying Ki-67 in ICPN specimens may provide valuable supplementary prognostic information. Cases with high Ki-67 (e.g., >25%) warrant exhaustive histologic sampling to exclude occult invasion and may benefit from enhanced clinical surveillance or staging work-up. Conversely, lesions with low Ki-67 (e.g., <15%), especially if associated with low-grade dysplasia and tubular/pyloric phenotype, may be managed more conservatively[2].

In our series, Cases 2 and 3 with extensive dysplasia and invasion would be anticipated to show elevated Ki-67 indices, while Case 4 with focal dysplasia and no invasion, and Case 5 with low-grade proliferation, would show lower Ki-67 values consistent with their benign or minimally dysplastic histology.

Practical Pathologic Reporting and Sampling Recommendations

Given the heterogeneity and clinicopathologic importance of ICPN, standardized histologic sampling and comprehensive reporting are essential. The following recommendations are based on established guidelines and the data presented herein[1][3]:

Complete specimen submission: Any gallbladder polyp ≥1 cm should be entirely submitted for histologic examination. Smaller lesions should also be submitted if clinically suspected or radiologically concerning.

Adequate sampling of adjacent mucosa: The normal-appearing mucosa distant from the polyp should be sampled from multiple sites (fundus, body, neck) to evaluate for coexistent dysplasia or adenoma-carcinoma transitions and to rule out separate invasive lesions.

Comprehensive histologic reporting: The final pathology report for any ICPN should document:

- Diagnosis of ICPN (when criteria are met)
- Size of the intramucosal lesion (in cm)
- Predominant architectural pattern (papillary, tubular, tubulopapillary) and percentage
- Predominant cell lineage (biliary, gastric pyloric, gastric foveolar, intestinal, oncocytic) with percentages
- Extent of high-grade dysplasia (absent, focal <25%, substantial 25-75%, extensive >75%)
- Presence or absence of invasive carcinoma, and if present: histologic type, size, pT stage (TNM 8th edition or later), and extent (focal, substantial, extensive)
- Lymphovascular invasion status
- Margin status (cystic duct, peritoneal surface)
- Immunohistochemical results including Ki-67 index (percentage of Ki-67-positive nuclei)
- Any ancillary molecular or genetic testing (if performed)

Immunohistochemical panel: For most ICPN cases, a panel including CK7, CK20, MUC1, MUC2, MUC5AC and CDX2 is recommended to establish cell lineage. Ki-67 should be quantified and reported as percentage of positive nuclei. Additional markers such as p53, KRAS mutational analysis and EGFR may be considered in cases with high-grade dysplasia or invasion to further characterize prognostic and therapeutic targets[2].

Reporting format: Use the ICPN framework rather than legacy terminology (adenoma, papillary carcinoma, etc.) to ensure clarity and consistency with recent literature and enable meaningful comparison across institutions and studies.

Clinical Management Implications

The recognition and accurate reporting of ICPN has significant implications for patient management. Several evidence-based recommendations emerge from the current literature[1,3]:

Surveillance and follow-up: Non-invasive ICPN without high-grade dysplasia and with low Ki-67 index may warrant close clinical and radiologic follow-up rather than immediate aggressive intervention, given their relatively low risk of progression.

Staging and treatment: ICPN-associated invasive carcinomas should be staged according to TNM criteria (8th edition or later) and treated in accordance with standard gallbladder cancer protocols. However, the prognostic advantage of ICPN-associated carcinomas compared with pancreatobiliary-type tumors suggests that stage-matched outcomes may be more favorable, which should be discussed with patients.

Molecular and genetic considerations: Given the overlap with pancreatic IPMN and biliary IPN in terms of histology and putative dysplasia-to-carcinoma progression, emerging evidence regarding molecular alterations (KRAS, TP53, SMAD4, etc.) in ICPN may eventually inform risk stratification and potentially guide targeted therapy[1,2]. However, molecular analysis remains investigational in routine ICPN assessment.

Multidisciplinary consultation: Cases with ICPN and associated invasive carcinoma should be reviewed in a multidisciplinary tumor board to optimize staging, adjuvant therapy recommendations and surveillance strategies.

CONCLUSION

Intracholecystic papillary-tubular neoplasms represent a distinct category of preinvasive gallbladder neoplasm with significant clinicopathologic and prognostic heterogeneity. The present case series illustrates the spectrum of ICPN presentation, ranging from low-grade lesions with minimal dysplasia to high-grade dysplasias with early invasive carcinoma. Architectural subtype (papillary/tubulopapillary vs. tubular), cell lineage (biliary/foveolar vs. gastric/intestinal), extent of high-grade dysplasia, lesion size, and Ki-67 proliferation index all contribute to risk stratification. Accurate histopathologic diagnosis and comprehensive reporting using the ICPN nomenclature facilitate comparison with published series, improve prognostication and guide clinical decision-making. Ki-67 enumeration, performed in conjunction with morphologic assessment, may provide valuable supplementary prognostic information to distinguish high-risk lesions requiring aggressive management from low-risk lesions amenable to conservative surveillance. Future studies incorporating larger patient cohorts, molecular profiling, and extended clinical follow-up data will further refine our understanding of ICPN biology, natural history and optimal therapeutic strategies. [17,20]

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