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Original Contribution

Intracholecystic papillary-tubular neoplasms of the gallbladder – A clinicopathological study of 36 cases

Kala Gnanasekaran Kiruthiga[a], Thomas Alex Kodiatte[a,*], Deepak Burad[a], Reshma Kurian[a], Ravish Sanghi Raju[b], Manbha Lamare Rymbai[b], Aparna Munjurpattu Jagannathan[b], Frederick Lorence Vyas[b]

[a] Department of General Pathology, Christian Medical College, Vellore, India
[b] Department of Hepatopancreatobiliary Surgery, Christian Medical College, Vellore, India

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ABSTRACT

Intracholecystic papillary-tubular neoplasms (ICPNs) account for < 0.5% of all cholecystectomies. There is a lack of significant published data from the Indian subcontinent on ICPN to the best of our knowledge. The objective of the current study was to describe the clinicopathological features of ICPN of gallbladder from the departmental archives during a 5.5-year period. We also aimed to classify them into various histological subtypes and to correlate the clinicopathological parameters of ICPN with invasive adenocarcinoma.

This study included 36 cases diagnosed over a period of 5.5 years (2013–2018). Clinical, radiological and histopathological data were analyzed in detail.

The incidence of ICPN was 0.8%. The mean age of patients was 45.7 years with a female to male ratio of 1.3:1. Biliary phenotype was associated with invasion ($p \leq 0.001$). Papillary pattern was present in 15 cases (41.6%) and was associated with invasion ($p \leq 0.001$). High grade dysplasia was seen in 34 cases (94.4%), of which invasion was seen in 18 cases (50%). One case in our study also had synchronous common bile duct carcinoma. Majority (92%) of the patients were alive and well at the end of available follow-up (mean of 7 months and 25 days).

ICPNs are mass forming neoplasms of the gallbladder with a slight female predominance. Biliary phenotype has an aggressive course, often associated with an invasive adenocarcinoma component. Papillary configuration of the lesion is significantly associated with an invasive component. Diligent follow-up of these lesions is warranted as they can be associated with other malignancies of the biliary system.

1. Introduction

In the pancreatobiliary tract, mass-forming tumors composed of preinvasive neoplastic cells presenting as clinically detectable (≥1.0 cm) masses are now classified under a unified category of intraductal papillary neoplasms (IPNs) in the bile ducts, intracholecystic papillary-tubular neoplasms (ICPNs) in the gallbladder, intra-ampullary papillary-tubular neoplasms (IAPNs) in the ampulla and intraductal papillary mucinous neoplasms (IPMNs) or intraductal tubulopapillary neoplasms (ITPNs) in the pancreas [1-6]. These tumoral intraepithelial neoplasms represent an "adenoma-carcinoma" sequence. Their clinicopathologic, immunophenotypic, and molecular characteristics, as well as biological behavior, are different from the nontumoral (flat)-type preinvasive neoplasms of the respective organs. They all share similar characteristics like exophytic nature, expression of cellular lineages (biliary, gastric, intestinal, oncocytic), and presence of a spectrum of dysplastic change (adenoma-carcinoma sequence), often occurring in varying degrees. They are distinct from the conventional invasive cancers of these sites for which they are often mistaken because of their mass-forming nature [1].

ICPNs encompass all mass-forming, preinvasive neoplasms ≥1.0 cm, recognized in the WHO-2010 classification as "adenoma" (tubular, papillary, pyloric gland, foveolar gland, biliary, intestinal, or otherwise) and "intracystic papillary neoplasms" (intestinal or pancreatobiliary) [1,6-10].

Due to the lack of uniformity in the terminology and defining characteristics, data on the clinicopathological features and natural history of this entity is not well established. There is a lack of many published data on it from the Indian subcontinent. In this context, the aims of the current study were to describe the clinicopathological

* Corresponding author.
E-mail address: thomaskodi@cmcvellore.ac.in (T.A. Kodiatte).

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features of ICPN of gall bladder from the departmental archives during a 5.5-year period, to classify them into various histological subtypes and to correlate the clinicopathological parameters of ICPN with invasive adenocarcinoma. This study also aimed to analyze other parameters that are associated with invasive adenocarcinoma and the survival of patients with this entity.

2. Materials and methods

This study was approved by the Institutional Review Board (Research and Ethics). This study did not directly involve human subjects and used formalin fixed paraffin embedded tissue blocks archived in the Department of Pathology. Hence, a waiver of consent was obtained.

A total of 36 cases of ICPN (all cases with lesions at least 1 cm in dimension wherever possible) diagnosed by the Department of Pathology at our tertiary care hospital, from January 2013 to July 2018 (5.5 years) were included in this study. Slides and blocks of all cases were retrieved. Twenty-six cases were in-house specimens and ten cases were second opinion slides and blocks for which the gross features were not easily available. The second opinion cases had a minimum dimension of 1 cm by microscopic examination and hence included. The hematoxylin and eosin stained sections of slides were reviewed and a detailed pathological analysis was done. This included the growth pattern of the lesion (papillary, tubular or tubulopapillary), cell lineage (biliary, intestinal, complex pyloric, mixed), presence or absence of dysplasia and grade of dysplasia (low versus high grade). The percentages of the growth patterns and cell lineages were also examined and a cut-off of > 75% volume of the whole lesion was used as pure predominant growth patterns or cell lineages [1]. If papillary growth pattern was < 75% and the secondary tubular pattern > 25%, then it was classified as tubulopapillary patterns. Each case was assigned a cell lineage predominant morphology if > 75% of cell population were of that cell lineage, otherwise, it was kept under mixed type [1]. In cases with high grade dysplasia (HGD), all sections were studied carefully for the presence or absence of invasive adenocarcinoma. For further categorization of the stage of tumor, the presence of lymphovascular and perineural invasion and the lymph nodal status (wherever available) were evaluated. The background gall bladder was assessed for the presence of chronic cholecystitis, intestinal and pyloric gland metaplasia, cholesterolosis and presence or absence of dysplasia.

The gross pathological findings recorded were the size of polyp, number of polyps, location in gallbladder (fundus, body or neck) and the type of polyp (sessile versus pedunculated) in the available macroscopically examined cases.

Relevant clinical details like the age, sex, presenting complaints and basic follow-up were noted from the electronic medical records.

Radiological findings including the size and number of polyps were also noted.

Descriptive data were summarized by frequencies and percentages for categorical variables using SPSS IBM software Version 22. Chi-square/Fisher's exact test was used to compare the association between categorical variables and a p-value of ≤0.05 was considered significant.

3. Results

3.1. Demography and clinical details

Of 4112 cholecystectomies, the incidence of ICPN in this study was 0.8%. The mean age (range) of the patients in this study was 45.7 years (range: 7–69). ICPN was slightly more common in females as compared to males (1.3:1) [Table 1].

The most common symptom was right-sided abdominal pain in 27 patients (75%). Jaundice was seen in 1 patient (3%), loss of weight and appetite in 1 patient (3%) and one other patient (child) (3%) had presented with an abdominal mass, ascites, and metachromatic leukodystrophy. The lesions in the gallbladder were incidentally detected in 6 other patients (16.6%) during evaluation for other systemic complaints. [Table 1].

Table 1
Comparison of demographic and important clinical characteristics among ICPN.

	ICPN without invasion (n = 18)	ICPN with invasion (n = 18)	p value
	n (%)	n (%)	
Age(years):			
< 50	11 (61.1%)	12 (66.7%)	0.73
> 50	7 (38.9%)	6 (33.3%)	
Sex:			
Male	10 (55.6%)	6 (33.3%)	0.20
Female	8 (44.4%)	12 (66.7%)	
Symptoms:			
Pain	13(86.6%)	14(93.4%)	
Jaundice	0	1(6.6%)	
Loss of appetite and weight	1(6.6%)	0	
Ascites	1(6.6%)	0	
Asymptomatic	3	3	
T stage:			
T1	NA	7(38.9%)	
T2	NA	10(55.5%)	
T3	NA	1(5.6%)	

In the 26 in-house cases, pre-operative radiological imaging revealed polyps in 18 cases (69%), nodular thickening in 4 (15%) and other diagnoses (no polyp) in the remaining four. Among the four other radiological diagnoses, sludge was reported in 2 cases, cholelithiasis in one case, and adenomyomatosis in the last one. The average radiological size was 2.35 cm (range: 1.1 to 6 cm) in 19 of the in-house cases. Detail on radiological size was not available in the polyps of 3 in-house cases.

At the time of pre-operative assessment, 31 cases (86%) underwent open or laparoscopic simple cholecystectomy, whereas 4 cases (11%) underwent initial frozen section cholecystectomy followed by completion radical cholecystectomy and one case was offered upfront radical cholecystectomy.

3.2. Gross findings [Table 2]

The gross findings were easily available for the in-house cases (26 of 36). The average gross size of the 26 examined cases was 2.77 cm (range: 1.0 to 8.5 cm).

In 81% (21 of 26) of cases, there was a single polyp and remaining 5 cases (19%) had multiple polyps. Macroscopically, out of 26 grossly examined cases, the polyps were sessile in 18 cases (69%) and

Table 2
Comparison of macroscopic characteristics of grossly available ICPNs (n = 26).

Gross characteristics	ICPN without invasion (n = 17)	ICPN with invasion (n = 9)	p-Value
	n (%)	n (%)	
Size (cm):			
< 3	11 (65%)	4 (45%)	0.42
≥3	6 (35%)	5 (55%)	
Polyp number:			
Single	14 (82%)	7 (78%)	0.58
Multiple	3 (18%)	2 (22%)	
Polyp type:			
Sessile	10 (59%)	8 (88%)	0.19
Pedunculated	7 (41%)	1 (11%)	

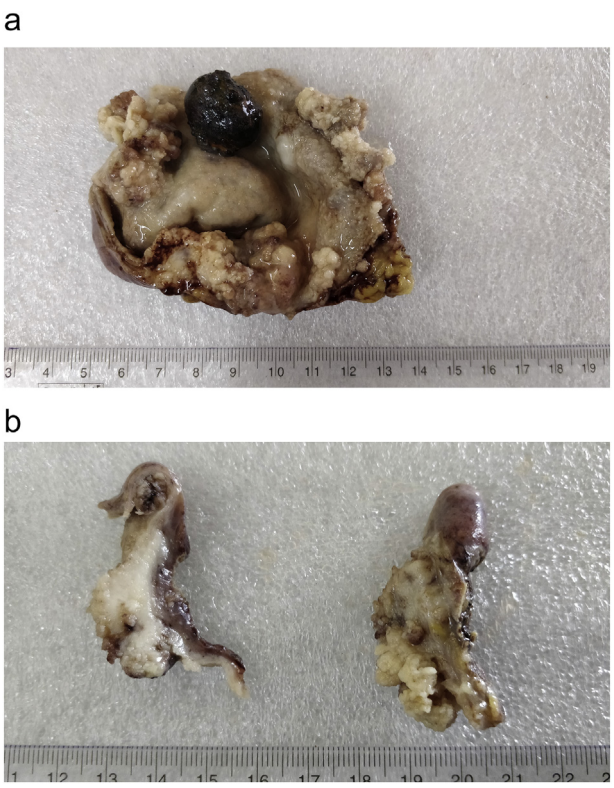

Fig. 1. Gross appearance of ICPN
(A) Exophytic papillary, sessile polypoid lesion distinctly seen along with a gall stone.
(B) Cut surface – Grey white area in the wall depicting invasion.

pedunculated in 8 cases (31%) [Fig. 1A, B].

Data on the gross findings of the ten second opinion cases was not available. Most single polyp lesions [9] were located in the body (35%), 7 cases in the fundus (27%) and 5 cases in the neck (19%). Remaining 5 cases had multiple polyps and hence located throughout the gallbladder.

3.3. Microscopic findings

Of the polyps, 16 (44.4%) had a tubular configuration, 15 (41.7%) had papillary and 5 (13.9%) had a tubulopapillary architecture [Table 3].

Table 3
Comparison of histologic characteristics among ICPN cases with and without invasion.

Pathological characteristics	ICPN without invasion (n = 18)	ICPN with invasion (n = 18)	p-Value
	n (%)	n (%)	
Growth pattern:			
Papillary	3 (16.6%)	12 (66.7%)	< 0.001*
Tubular	14 (77.8%)	2 (11.1%)	
Tubulo-papillary	1 (5.6%)	4 (22.2%)	
Cell lineage:			
Biliary	4 (22.3%)	14 (77.8%)	< 0.001*
Intestinal	1 (5.5%)	3 (16.7%)	
Complex pyloric	11 (61.1%)	0 (0%)	
Mixed	2 (11.1%)	1 (5.5%)	
Dysplasia:			
Low grade	2 (11.1%)	0 (0%)	0.49
High grade	16 (88.9%)	18 (100%)	

The most common cell lineage was biliary [Fig. 2A], seen in 18 cases (50%), followed by complex pyloric non-mucinous [Fig. 2B] in 11 (30.6%) cases, intestinal [Fig. 2D] in 4 (11.1%) cases, and mixed cell lineages in 3 (8.3%) cases. Squamous morules were seen in all cases of the complex pyloric gland phenotype [Fig. 2C]. The mixed types included the patterns described above with gastric foveolar [Fig. 3A] and gastric pyloric [Fig. 3B] type cells in some of the cases. One of the cases also had extensive foamy gland pattern [Fig. 3C]. The oncocytic type was not seen.

HGD was present in 34 cases (94.4%) of which, 18 cases (52.9%) were associated with invasion [Fig. 3D] (50% overall cases) [Table 3]. One case also had synchronous common bile duct carcinoma.

3.4. Comparison of demographic and histological parameters with invasion

Fifteen of 30 symptomatic ICPN patients had associated invasion. In the 27 ICPN patients who presented with right-sided abdominal pain, fourteen (52%) had associated invasion [Table 1]. Three of the 6 incidentally detected ICPNs also had associated invasion.

Of the 18 cases with invasion, 7 cases (38.9%) were pT1 (6 pT1a and 1 pT1b), 10 cases (55.5%) were pT2 and 1 case (5.5%) was pT3 [Table 1]. Lymphovascular invasion was seen in 1 case and perineural invasion in 2 cases.

Of the 18 cases with invasion, 10 (55.5%) were initially offered standard treatment according to the pre-operative assessment, i.e., 5 were simple cholecystectomies (5 pT1a) and 5 (3 pT2, 1 pT3 and 1 pT1a) had been offered radical cholecystectomies. Of the remaining 8 cases (six second opinion cases and two in-house ones), who were offered initial simple cholecystectomies, one had pT1b and seven had pT2. Radiology data that were available in these two in-house cases had shown only cholelithiasis (no polyp) in one case and nodular thickening of 2 cm in the other case.

When the cell lineages were compared with invasion, the biliary phenotype was significantly associated with invasion ($p \leq 0.001$). Similarly, when the architectural pattern was assessed for invasion, papillary architecture was significantly associated with invasion ($p \leq 0.001$) when compared to tubular and tubulopapillary types [Table 3].

3.5. Background gall bladder

Background gallbladder showed features of chronic cholecystitis in 33 cases (83%), pyloric metaplasia in 8 cases (22.2%), intestinal metaplasia in 7 cases (19.4%), cholesterolosis in 3 cases (8.3%), flat high-grade dysplasia in 7 cases (19.45%) and flat low-grade dysplasia in 2 cases (5.5%).

There was no significant difference in the age and sex of the patient and size of the lesion in cases with or without invasion [Tables 1, 2].

3.6. Survival analysis

One patient presented with metastatic peritoneal disease at initial presentation (pT2). Mean (range) follow-up period was 7 months and 25 days (6 days to 40 months and 8 days). Nine (50%) of the 18 non-invasive ICPN patients only had a short mean (range) follow-up period of 11 days (6 to 25 days). Of 8 patients who had initially undergone simple cholecystectomy with pT1b and above, 4 patients were offered completion radical cholecystectomy at a later date during the follow-up. Remaining 3 patients were lost to follow-up and one other patient was not surgically fit for intervention. Majority (33; 92%) of the patients including the one patient with the initial presentation of metastatic peritoneal disease were alive and well at the end of available follow-up. Three other patients presented with metastatic disease during follow-up and the various sites of metastasis included port site, liver (multiple) and thoraco-abdominal lymph nodes. One of these patients with metastasis also had the synchronous common bile carcinoma

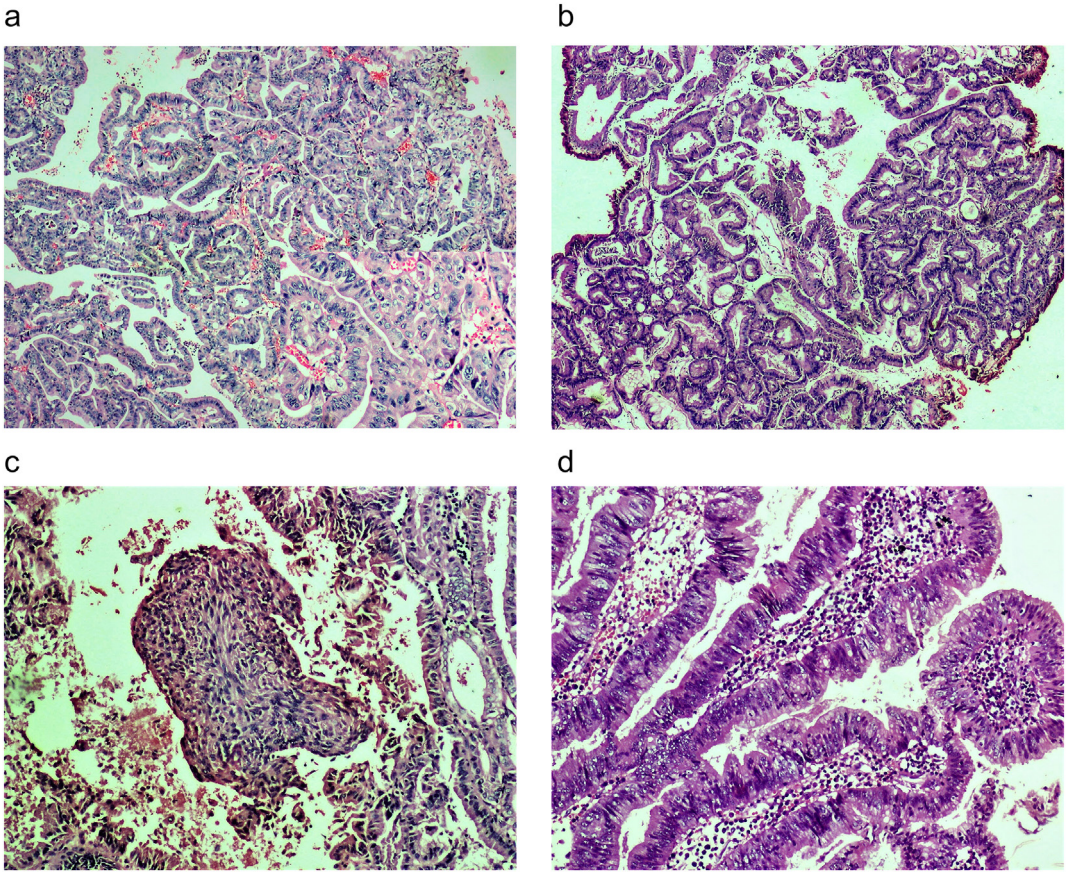

Fig. 2. Microscopic subtypes of ICPN
(A) Biliary: Papillary-tubular architecture with cuboidal cells exhibiting nuclear pseudo-stratification, hyperchromasia and atypia (H&E X 40 main and H & E X 200 inset)
(B) Complex pyloric non-mucinous: Closely packed small tubular structures, some of which are dilated (H&E X 40)
(C) Squamous morule: Whorls of spindle shaped cells seen in the complex pyloric non-mucinous subtype. (H&E X 100)
(D) Intestinal: Papillary/Villous structures lined by columnar cells with elongated cigar shaped nuclei and pseudostratification (H&E X 100).

and was the only patient who had expired in this study. Four patients (11%) had also undergone chemotherapy after the first surgery.

4. Discussion

Intracholecystic papillary-tubular neoplasms (ICPNs) are mass-forming neoplasms (≥1 cm) that are the gallbladder counterparts of the pancreatic IPMNs, ampullary IAPNs and the biliary ductal IPNs [1,11]. ICPNs are rare and their incidence in the current study was 0.8%, as compared to the studies done by Adsay et al. and Argon et al. where they were < 0.5% [1] and 0.6% [9] respectively. The female: male ratio was 1.3:1 which is similar to the other studies [1,9] and the mean age was 45.7 years (range 7–69) which was lower than the 61–69 years in other studies [1,9,10]. The only pediatric case in the current study was a case of metachromatic leukodystrophy. Causal association of ICPN or gall bladder polyposis with metachromatic leukodystrophy has been described, hypothesized by prolonged contact with sulfatides in bile [12-14]. Although ICPNs are usually seen in the elderly, there is also a published report of ICPN occurring in a 15-year-old female [15].

Most of the patients in our study presented with abdominal pain, which is similar to the observation by Adsay et al. [1]. Of the 26 in-house cases, pre-operative radiological imaging revealed polyps or nodular thickening in 22 cases (85%) and in the remaining 15%, the polypoidal lesion was missed.

Macroscopically, ICPNs arose more commonly in the body of gall-bladder, with a mean gross size of 2.77 cm and maximum dimension of 8.5 cm. They were characterized by single or multifocal large pedunculated or sessile exophytic cauliflower-like growths or by smooth-surfaced polypoid projections [1].

Microscopically, there were varying ranges of cytological atypia (dysplasia), architectural atypia with papillary and tubular patterns and also with cell lineages. Close to half of the cases (42%) were predominantly papillary similar to other studies by Adsay et al. and Argon et al. [1,9]. The frequency of HGD and associated invasive carcinoma was significantly higher in those with papillary growth pattern than in tubular ones, which was also observed by Adsay et al. [1]. In many cases in our study, dysplastic nature of the lesion was easily identified by the degree of cytological atypia. HGD was seen in close to 95% (34) of cases and manifested most commonly as cells exhibiting pseudostratification of nuclei, loss of polarity and nuclear pleomorphism. Few other HGD cases had a cribriform pattern, clear cell morphology with central nuclei and solid areas with comedo-necrosis.

In concordance with previously described literature, the pyloric complex non-mucinous phenotype lacked obvious cytologic atypia and the dysplastic nature was determined by the high nucleo-cytoplasmic ratio of cuboidal cells and the compact back-to-back arrangement of glands with no intervening stroma [1].

Many cases of the pyloric complex non-mucinous phenotype were uniformly complex without any mucinous component and few probably could be a high-grade transformation of the mucinous phenotype [1]. None of the ICPNs with a complex pyloric phenotype was associated with invasive carcinoma in our study despite their complex architecture. Adsay [1] noted that this phenotype was associated with carcinoma in about 18% cases.

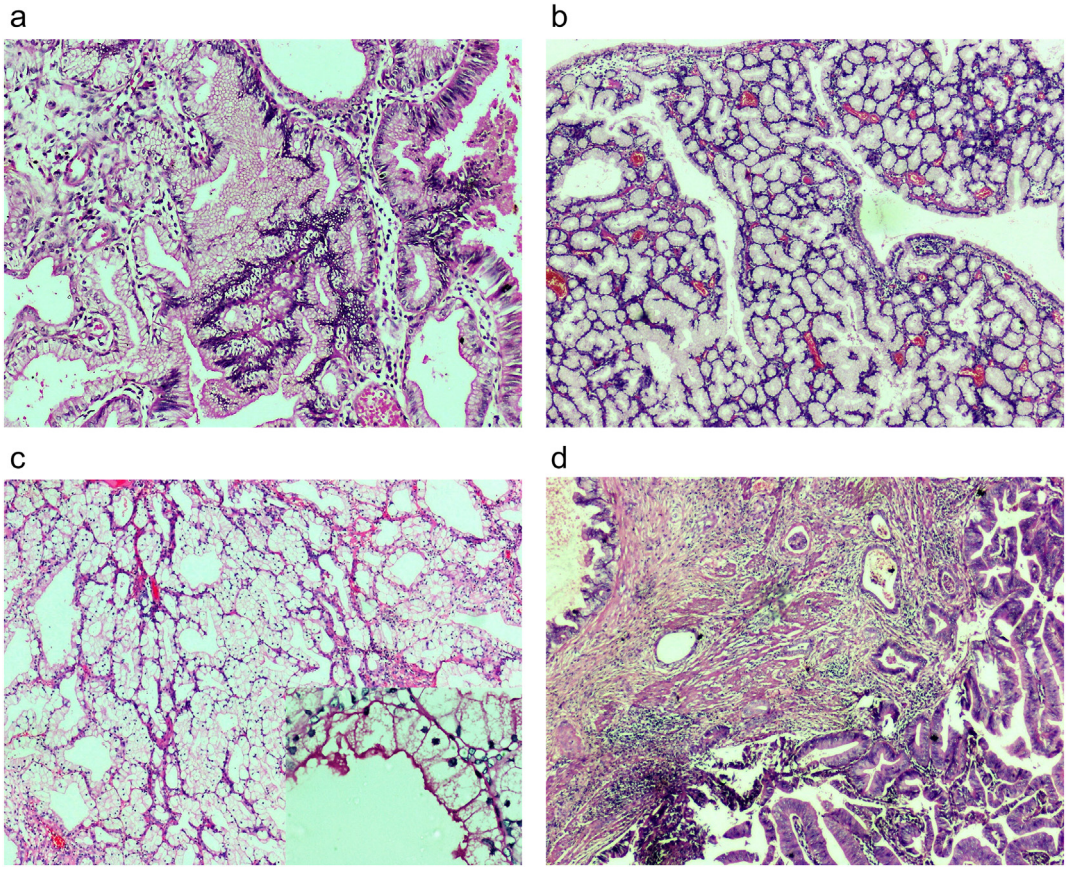

Fig. 3. Microscopic subtypes of ICPN
(A) Gastric foveolar: Glands and interconnecting tubules lined by columnar cells with abundant pale cytoplasm and basal nuclei resembling foveolar/endocervical epithelium (H&E X 100)
(B) Gastric pyloric: Small uniform glands which are tightly packed and contain abundant mucin. (H&E X 40)
(C) Foamy gland pattern: Closely packed small glands with a clear/ foamy cytoplasm. PASD stain (inset) highlights the apical mucin. (H&E X 40 main and PASD X 400 inset)
(D) Invasive adenocarcinoma: Atypical glands seen infiltrating into the muscular layer. (H&E X 40).

On the basis of the predominant pattern, 50% of ICPNs in the current study were of the biliary type. Apart from having a resemblance to gallbladder epithelium or pancreatobiliary-type IPMNs, this type also exhibits variants including clear cell and more columnar intestinal-appearing cells and are found to express MUC1 [1]. It was interesting to note that one of the cases in the current study with the pancreatobiliary phenotype, had shown extensive foamy gland type of cell morphology (Fig. 2H). This type of morphology is noted in the foamy gland variant of pancreatic ductal adenocarcinoma.

The second cell lineage, gastric phenotype has two distinct types: the foveolar and pyloric type. The former has uniform MUC5AC expression [1], often admixed with biliary phenotype and is commonly accompanied by invasive carcinoma (in 60% of the cases). The pyloric type, is characterized by diffuse MUC6 expression [1], and is usually large, homogenous with squamous morule formation, and has a significantly lower frequency of associated invasive carcinoma (18%). Some examples of this type are similar to pancreatic ITPNs, because of tubular growth, MUC6 expression and non-mucinous cytomorphology [1]. In the current study, these gastric foveolar phenotypes were seen in combination with other phenotypes and were not seen as the predominant pattern in any of the cases. It has also been noted that the non-mucinous type is often associated with a relatively clean background and forms complex, pedunculated multinodular intraluminal tumors that detach very easily and may be dismissed as necrotic debris on the grossing table [1]. This feature was noted in four of our ICPNs. Also, these ICPNs had nuclear overlapping and chromatin clearing resembling papillary thyroid carcinomas, similar to as described in other studies [1]. Morule formation was most commonly encountered and was seen almost exclusively in this type which was also observed by Adsay et al. [1]. In view of the morule formation, the concept of molecular association with estrogen activated beta-catenin pathway alteration may be seen in the pyloric-type ICPNs [1,16]. However, this warrants further investigation.

Intestinal lineage was seen in around 11% of the cases in the current study, which was similar to the other studies [1]. A rare phenotype is the oncocytic phenotype ICPN, consistently showing MUC1 expression and often negative for HepPar-1 and MUC6 expression [1]. This phenotype was not seen in the present study.

Invasive carcinoma was seen in half or more than half of the ICPNs at the time of diagnosis, which was also seen in other studies [1] and most of these were pancreatobiliary-type gallbladder adenocarcinomas.

As per the pTNM staging system [17,18], among those with invasive ICPNs, 38.9% had pT1, 55.5% had pT2 and 5.6% had pT3 lesions and our results are similar to previous literature [10,19-21].

The gastric pyloric mucinous phenotypes resemble the polypoid pyloric gland metaplasias in the gallbladder, but with strict criteria of 1 cm, both can be differentiated [1]. Few small metaplastic and hyperplastic lesions (< 1 cm) mimic ICPNs [8].

Majority (92%) of the patients were alive and well at the end of available follow-up (mean of 7 months and 25 days). Remaining three patients (8%) presented with metastatic disease during follow-up (port site, liver and thoraco-abdominal lymphnodes) and of which, one

patient had also died. The prognosis for ICPNs is better than that for other invasive carcinomas of the gallbladder [1,8]. Noninvasive cases have a better prognosis with 3- and 5-year survival rates being 90% and 78%, as compared to only 60% in invasive carcinoma [1].

ICPNs with associated invasive carcinoma have a better prognosis than pancreatobiliary-type gallbladder carcinomas (without ICPN), and this survival was independent of size and continued even with stage-matched comparison. Hence, ICPN-associated invasive carcinomas may have distinct biological properties [1].

One out of 36 cases in the current study had a synchronous common bile duct carcinoma. Late recurrences or adverse outcome in non-invasive ICPNs have been recorded, however extensively the cases are sampled and invasion is ruled out [1,8,15]. This is attributed to the field-effect or "field-defect" phenomenon resulting in a propensity to develop biliary tract carcinomas, similar to non-invasive pancreatic IPMNs [1,22-24]. This phenomenon is also observed for flat, non-tumoral high-grade dysplasia [1,8]. In the study done by Adsay et al. [1], 4 patients out of 55 non-invasive ICPNs had died of cancer, 3 of which were reported by imaging and biliary obstruction signs as biliary tract cancer. These occurred after a median of 73.5 months after the diagnosis of ICPN suggesting a new primary in the remaining biliary tract [1]. In the current study, 9 (50%) of the 18 non-invasive ICPN patients only had a short mean (range) follow-up period of 11 days (6–25 days). Hence, it needs to be stressed out that surgeons are aware of this biological entity and these patients ought to be kept under longer surveillance.

The limitations in the current study were the small sample size for prognostication, non-availability of pre-operative radiological data on the ten second opinion cases, short follow-up period and absence of availability of MUC (mucin) immunohistochemical markers.

5. Conclusion

ICPNs can be regarded as the gallbladder counterpart of the pancreatic IPMNs. There is an increased risk of developing biliary tract carcinomas in these patients and hence warrant a close follow-up and surveillance. There is an association of ICPNs with metachromatic leukodystrophy. Therefore, it is essential to identify this distinct biological subset of neoplasms in a specimen.

Declarations of interest

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Contributions

(I) Conception and design: KG Kiruthiga, TA Kodiatte; (II) Administrative support: TA Kodiatte; (III) Provision of study materials or patients: TA Kodiatte, D Burad, RS Raju, FL Vyas (IV) Collection and assembly of data: KG Kiruthiga, TA Kodiatte, R Kurian, AM Jagannathan; (V) Data analysis and interpretation: All Authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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