CASE REPORT

Intracholecystic Papillary Neoplasm (ICPN) of the Gallbladder. A Case Report.

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ABSTRACT

In the WHO Classification of Tumours of the Digestive System (2019), intracholecystic papillary neoplasm (ICPN), a pre-invasive neoplasm of the gallbladder, is described as non-invasive epithelial neoplasm with macroscopically discernible mass of pure papillary, tubular or tubulo-papillary architecture. The mass-forming characteristic of ICPNs in the gallbladder is radiologically similar to that of invasive tumours. Case report: A 58-year-old man presented with vomiting and prickling epigastric pain for two days. An abdominal CT scan showed a gallbladder tumour associated with dilated intrahepatic and common bile ducts. A wide-base polypoid tumour with papillary surface projection of 30 x 20 x 10 mm dimensions was present. Microscopically, a tubulo-papillary glandular tumour with high grade dysplastic foci and glandular areas with prominent intracellular mucin was seen. The adjacent mucosa displayed features of chronic cholecystitis, including pyloric metaplasia. After thorough sampling, there was no evidence of muscle infiltration, architectural complexity or perineural invasion. A diagnosis of intracholecystic papillary neoplasm with high grade dysplasia of the gallbladder was made. Discussion: The incidence of pre-invasive gallbladder neoplasms such as ICPN is less than 1% in a few studies, making them quite uncommon. It might be mistakenly identified radiographically as an invasive malignancy since it is forming a mass. In ICPN, the increase prevalence of diffuse high-grade dysplasia, papillary architecture, and biliary phenotype are linked to an increased risk of invasive malignancy. Nevertheless, gallbladder carcinoma with ICPN has better prognosis than those without.
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INTRODUCTION

Preinvasive neoplastic lesions known as intraepithelial neoplasia are seen throughout the digestive tract. Intramucosal pre-invasive lesions equal or larger than 1 cm in diameter with papillary or polypoid growth in the gallbladder were classified previously as intracystic papillary-tubular neoplasms in one study in 2012 (1). In the current WHO Classification of Tumours of the Digestive System (2019), it is known as intracholecystic papillary neoplasm (ICPN), described as non-invasive epithelial neoplasm with macroscopically discernible mass arising from the mucosa projecting into the lumen of the gallbladder (1).

Along with biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasm, they are recognised as preinvasive neoplasms in the gall bladder and extrahepatic bile duct (EHBD) (1). These lesions show similar characteristics that include exophytic nature with exception of the non-tumoural (flat)-type BilIN, expression of cellular lineages (biliary, gastric, intestinal, oncocytic), and presence of a spectrum of dysplastic change, often occurring in varying degrees. Pyloric gland adenoma (PGA) in the gallbladder that was previously included in the ICPN group, was currently categorised under a separate entity. It is considered as benign epithelial tumour that plays a minor role in the pathogenesis of gallbladder carcinoma (1). It is mostly suggested that ICPN tumorigenesis represents the 'adenoma-carcinoma' sequence (2).

Several studies indicate a range of 6-28% of ICPNs were associated with invasive carcinoma of the gallbladder. Increased association with invasive cancer were discovered in those with papillary and tubulo-papillary growth pattern, diffuse high-grade dysplasia, and a predominance of biliary and foveolar phenotype (2-4). Therefore, when these features are present in ICPN, thorough specimen sampling is necessary to rule out invasion. Even so, ICPN with an invasive component

is associated with a favourable prognosis than those of conventional gallbladder carcinoma without an ICPN component (1,2).

CASE REPORT

This is a case of 58-year-old man who came with a history of prickling epigastric pain of two days duration, relieved by bending forward. It was associated with vomiting. A gallbladder tumour was discovered on computed tomography (CT) scan of the abdomen, along with common bile duct and intrahepatic duct dilatation. There was however no gall stones identified and the patient did not present with jaundice. He then underwent cholecystectomy as gallbladder cancer was suspected.

Macroscopically, there was a 'stuck on' sessile polypoid tumour at the body of gallbladder with broad base and distinct from the surrounding gallbladder mucosa. Papillae projections on the surface of the tumour were observed. The tumour measures 30 x 20 x 10 mm in size (Figure 1). It was 20 mm away from the neck surgical margin whilst of 5 mm distance from the non-peritonealised margin. The surrounding gallbladder wall measures from 1 mm to 5 mm in thickness. The mucosa surrounding the polypoid tumour appears slightly thickened. Microscopic examination showed conglomerated type tubulo-papillary glandular neoplasm, composed mostly of biliary type tubular glands (<75%) as well as gastric foveolar type epithelium (>25%) (Figure 2A-C). High grade dysplasia was seen focally. Otherwise, there was no architectural complexity such as cribriform or solid formation, lymphovascular invasion or perineural invasion present. Extensive sampling leading to submission of all tumour tissue revealed no invasion into the muscularis propria, although involvement of the Rokitansky-Aschoff sinuses was present (Figure 2D). Adjacent to the tumour, random foci of pyloric metaplasia and features of chronic cholecystitis were present. A diagnosis of intracholecystic papillary neoplasm with high grade dysplasia of the gallbladder was made. Patient has been well and stable upon eight years of follow up postoperatively.

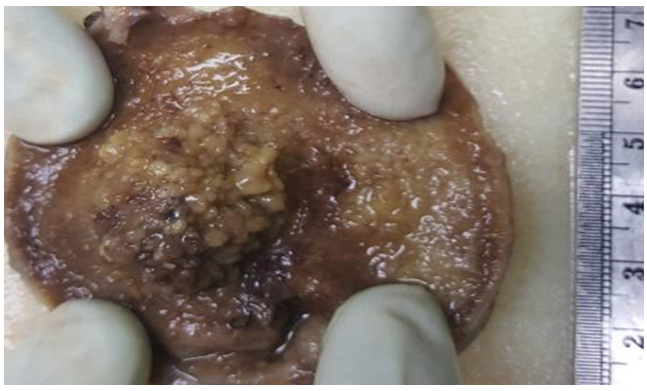

Figure 1: Distinct polypoidal growth with papillary projections measuring 3x2x1cm.

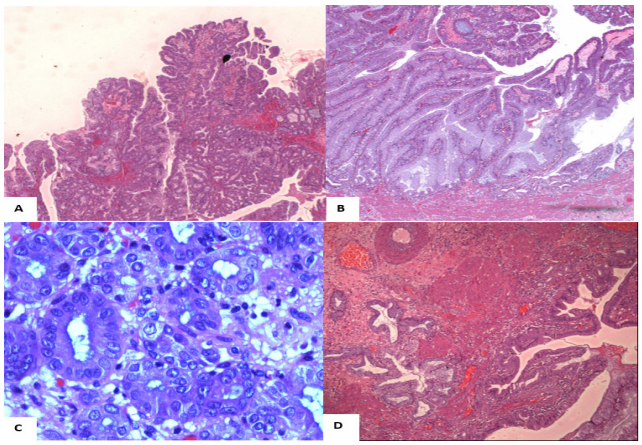

Figure 2: A. Tubulo-papillary growth pattern arising from the mucosa of gallbladder (H&E, x20). B. Papillary growth with mucin containing epithelium (H&E, x40). C. High grade dysplasia in tubular glands of biliary type featuring enlarged pleomorphic rounded nuclei with prominent nucleoli (H&E, x400). D. Involvement of Rokitansky Aschoff sinuses by ICPNs (H&E, x40).

DISCUSSION

Incidence and mean age of occurrence

According to earlier studies, the incidence of ICPNs among all cholecystectomies performed were low (<1%) (1-3). Prior to surgery, its radiological findings were indistinguishable from gallbladder malignancy. The incidence of ICPN among all cholecystectomies resected for non-neoplastic and neoplastic pathology in an earlier study was reported as 0.4% (1). This does not differ much from other series, which reported between 0.61-0.8% (2,3). Nonetheless, a recent study by Japanese researchers revealed a slight rise in incidence (1.5%) of ICPN among their cholecystectomies (4). On the other hand, according to a few literatures, 5 to 28% of ICPN was found among resected gallbladder adenocarcinoma (1,4,5) which may further emphasize the role of ICPN in its progression to invasive carcinoma. The mean age of patient diagnosed with ICPN ranges from 45 to 75 years old in a few studies (Table I), with somewhat higher frequencies among females (1-3,5). The patient age in this case study is within the reported range.

Clinical presentation and tumour size

According to a few case reports and studies, ICPNs may be discovered as an incidental finding without apparent symptoms (2). Radiologically, ICPNs mostly presents as polypoid lesions (2). Abdominal pain was the common presenting symptom in some studies however it was stated in the 2019 WHO classification of Tumours of Digestive System that both abdominal pain and incidental findings were equally common (1,2,5). In our case, vomiting episodes and epigastric pain were the earliest symptoms. The mean tumour size from other selected studies (Table I) ranges from 26 to 28 mm, which is comparable to our case. This size fulfilled the diagnostic criteria initially proposed by an earlier study, strictly adhering to the >=1 cm size which was not specifically defined for other lesions in

the gallbladder such as BilIN and PGA (1,2). On the contrary, the current WHO classification of Tumours of Digestive System 2019 did not provide size limitation in its definition. This size criterion may reinforce the idea that ICPNs are preinvasive tumours, as opposed to other benign hyperplastic or metaplastic lesions, which are often smaller (<1 cm) in size (1,2).

Table I: Selected studies (2016-2021) on ICPN of gallbladder.

No.	Author*	No of cases**	Mean Age (Year) (Range)	Symptom***	Mean Tumour Size (mm) (Range)	Associated Invasion #(%)
1.	Argon et al. (2016)	45	63 (32-87)		(27.6-43.9)	55.6
2.	Kiruthiga et al. (2019)	36	45.7 (7-69)	Abdominal pain, Asymptomatic	27.7 (10-85)	50.0
3.	Akita et al. (2019)	7	72 (61-78)	Epigastric pain Jaundice	26 (4-80)	57.1
4.	Nakanuma et al. (2021)	38	75 (49-94)		28 (13-43)	36.8

*Name of first author. ** Number of ICPN cases studied. ***Most common symptom #Proportion of ICPN associated with invasion.

Histomorphology, pathogenesis and molecular evidence

The histological characteristics of ICPNs range from pure papillary or tubular glands to a combination of tubulo-papillary architecture. An earlier study put forth the category of predominant architecture either pure papillary or pure tubular if there is >75% of the dominant architecture (tubular or papillary) and <25% of the secondary architecture. A mixed tubulopapillary architecture is indicated when the amount of these archtectures are between 25% to 75% (2,3). Architectural pattern such papillary and tubulopapillary were also found to be associated significantly with high grade dysplasia and invasive carcinoma of the gallbladder (p=0.008, p=0.005) respectively (2,3). This is also a feature that may differentiate ICPNs from PGA which is composed of predominantly tubular architecture with pyloric gland phenotype that showed diffuse MUC6 expression.

The variety of cell lineages in ICPNs include pancreaticobiliary, intestinal, gastric, and oncocytic phenotypes, where biliary lineage is more prevalent (1-4). Similar variation of cell lineages are also present in IPMN of the pancreas and IPNB of biliary system (1,2). The gastric and intestinal phenotypes may suggest a role of intestinal metaplasia in the tumorigenesis of ICPN. According to the degree of nuclear pleomorphism, polarity, and largest dimension, dysplastic alterations in ICPNs were divided into two categories: low grade and high grade (1,2). Although the typical characteristics of cytologic atypia are absent in some, such as those exhibiting pyloric phenotype, the sheer size and compact back-to-back proliferation of glands characterised the dysplasia (2). Immunohistochemical markers are not required for diagnosis, they can however, be utilised to document the most common cell lineages such as MUC 1 (biliary), MUC 2/CDX2/CK 20 (intestinal), MUC5AC (gastric foveolar), and MUC 6 (pyloric) (3,4).

Several conglomerated polypoid lesions are more common compared to the solitary polypoid lesion (4). ICPN also contained components of low-grade dysplasia and high-grade dysplasia with progression to invasion suggesting the role of adenoma-carcinoma sequence in its tumorigenesis (2). More studies are required to further elucidate its tumorigenesis. There is no significant association between the presence of prior cholecystitis or cholelithiasis with ICPN incidence as compared to PGA (1,4). Similar to IPMN of the pancreas and IPNB in the biliary tract, ICPN also shows KRAS mutation, although GNAS and p53 mutations are less common. Mutations of STK11 and CTNNB1 were found solely in ICPNs in previous literature (5). On the contrary, frequent TP53 mutation were present in papillary carcinoma of the gallbladder (3,5).

Factors associated with invasive carcinoma and mimicry

Most prior studies reported ICPN is associated with invasive carcinoma in >50% of cases (Table I). The amount of high-grade dysplasia, whether localized or diffuse, is one of the few factors that are linked to a higher risk of invasion. One study found a statistically significant association (p=0.002) between the incidence of invasive malignancy and diffuse high-grade dysplasia (3). Papillary architecture is also found to be associated with a higher incidence of invasive carcinoma than tubular architecture (2). With regards to cellular phenotype in ICPN, biliary and foveolar phenotype predominance has been associated with a higher prevalence of invasive carcinoma (1,2). Therefore, in the presence of these features, thorough specimen sampling to rule out invasion may be warranted.

Sometimes ICPN's involvement of the Rokitansky Aschoff (RA) sinus may be misdiagnosed as an invasion of the underlying muscularis propria (1). Rokitansky Aschoff sinuses were created when the mucosal epithelium invaginated into the muscle layer as a result of elevated intraluminal pressure. They present a problem for diagnosis since it may be difficult to differentiate between neoplastic cells involving the RA sinuses and those with true stromal invasion. Accurate clinicopathological analysis and thorough specimen evaluation is therefore essential.

Prognosis of ICPN with and without invasion

As a precursor lesion, patients with ICPN alone had a better chance of surviving compared to those who had

papillary gallbladder carcinoma (5). This is probably related in part to the early detection of pre-invasive carcinoma and in part explained by the variations in their biologic behaviour. In a study of 76 resected gallbladder neoplasms, 32 cases present with papillary growth and 7 were diagnosed with ICPN. None of these 7 cases experienced cancer-related death or recurrence (5). In addition, cases of invasive gallbladder adenocarcinoma with components of ICPN showed better prognoses than those without, indicating that there may be a biological difference between invasive carcinoma associated with exophytic papillary neoplasia (ICPN) and that without such lesions (1,2,5). A comparison between ICPN with associated gallbladder papillary carcinomas and conventional gallbladder adenocarcinoma revealed more frequent mucin hypersecretion, reduced lymphovascular invasion, and nodal metastases in the former (5). A subgroup of ICPNs from one study also had mucin hypersecretions which were not associated with stromal invasion (4).

CONCLUSION

As a conclusion, ICPN is one of the rare pre-invasive neoplasms in the gallbladder recognized in the WHO Classification of Tumour of Digestive Tract 2019 which is similar to its more widely recognised counterparts, IPMN of the pancreas and IPNB of the biliary system. The relative rarity of ICPN parallels the fact that there is little scientific knowledge on precursor lesion of gallbladder carcinoma. It may be characterised by a mixture of cellular lineages, a combination of papillary or tubular growth patterns as well as different grade of dysplasia. It is relatively an indolent precursor with better prognosis compared with non-tumoural pre-invasive neoplasm such as BilIN (1). Presence of ICPN in association with gallbladder adenocarcinoma have also been shown to be associated with better prognosis compared to conventional gallbladder adenocarcinoma without ICPN. Hence, it is essential to be familiar with this preinvasive neoplasia in the gallbladder which requires a comprehensive clinicopathological evaluation that will lead to conscientious patient management.

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