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Case Report

Pathology Section

Intracholecystic Papillary Neoplasm with Low-grade Intraepithelial Neoplasia: A Rare Entity

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ABSTRACT

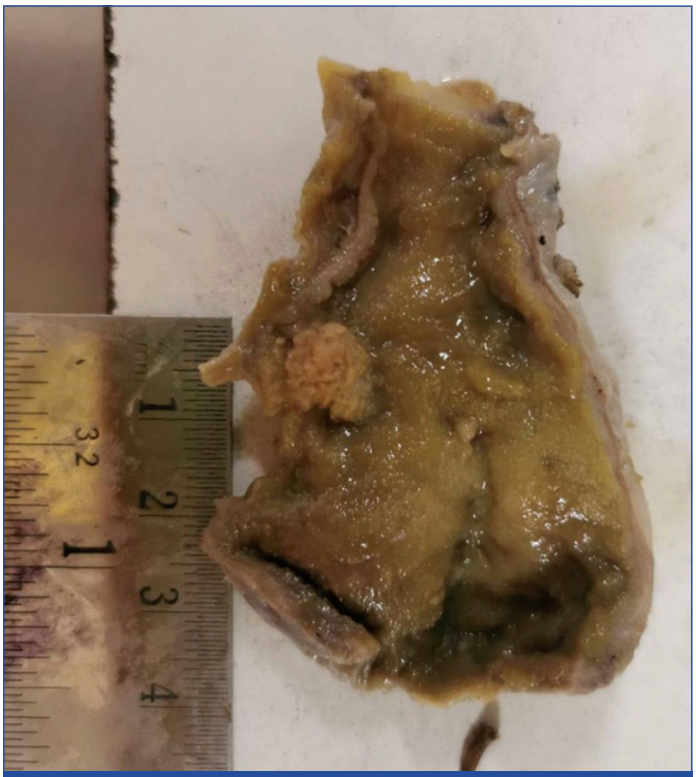
Intracholecystic Papillary Neoplasm (ICPN) is a recently described, rare, mass forming, epithelial neoplasm originating in the mucosa of the gall bladder. It usually protrudes in the lumen and is generally non invasive, but may show dysplastic changes which may be low-grade or high-grade or may be associated with invasive carcinoma. Authors, hereby, describe a case of ICPN in a 57-year-old female patient who reported to Surgery Outpatient Department (OPD) with the chief complaint of pain in abdomen since last five days. On ultrasonography, gall stones were detected for which she underwent cholecystectomy. Histopathological Examination (HPE) revealed a papillary growth in the body of gall bladder measuring 1.0 cm in diameter. Sections from the growth showed back-to-back arranged glands exhibiting a papillary pattern. The glands were lined by columnar epithelium with basally located nuclei. Pyloric metaplasia was noted focally. No foci of invasion were seen. Papillary hyperplasia was noted in adjacent areas along with features consistent with chronic cholecystitis. Thus, a diagnosis of ICPN with low-grade intraepithelial neoplasia was made. The patient recovered well postsurgery and is on regular follow-up.

Keywords: Dysplasia, Gall bladder, Invasive carcinoma, Polypoidal

CASE REPORT

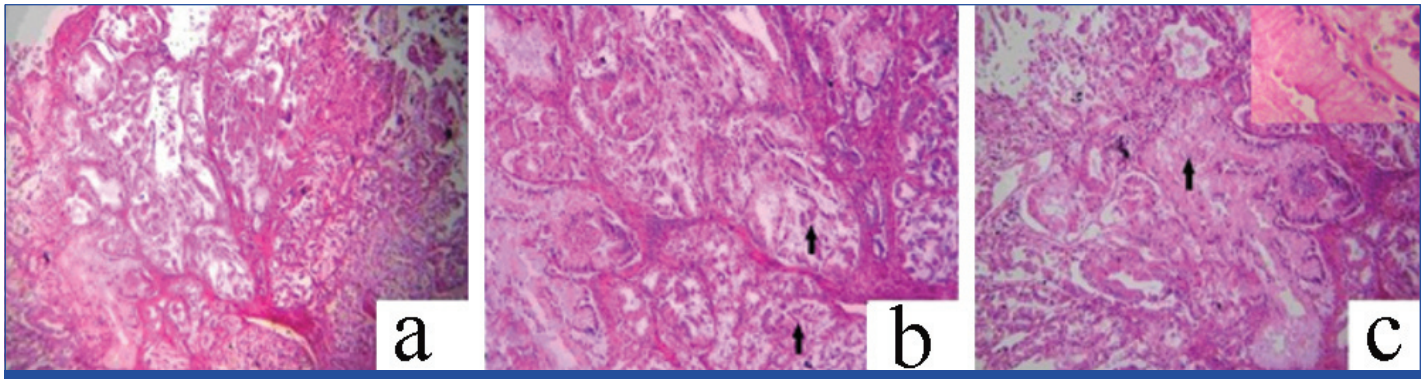
The present case is of a 57-year-old female patient who was admitted in the Surgery Ward with the chief complaint of dull pain in abdomen since last five days. There was no other relevant present or past medical history. The patient was afebrile and on physical examination, mild tenderness was detected in right hypochondrium. Ultrasound findings included fatty change liver (grade 1) and gall stones. Complete blood count revealed mild anaemia (haemoglobin was 10.9 gm/dL). Her other routine investigations were within normal limits except for slightly raised serum alkaline phosphatase (154 U/L).

On the basis of clinical, laboratory and radiological findings, a provisional diagnosis of cholecystitis with cholelithiasis was made. Cholecystectomy was performed, which was uneventful. Operative findings included friable liver bed, thick-walled gall bladder with multiple adhesions with short cystic duct and a solitary stone impacted at the neck. Post surgery patient was administered intravenous fluids and prescribed injectable antibiotics and antacids. Cholecystectomy specimen was sent for Histopathological Examination (HPE). On gross examination, gall bladder measured 8.0×3.0×3.0 cm. On cut section, a papillary, pale yellow, sessile growth was seen in the body of the gall bladder measuring 1.0 cm in diameter. Adjacent mucosa was velvety and bile stained. Wall thickness measured 0.5 cm [Table/Fig-1]. A cholesterol stone was received in the container. Haematoxylin and Eosin (H&E) stained sections from the papillary growth showed proliferating glands arranged in papillary pattern with thin fibrovascular core. The glands were lined by columnar epithelium with basally located nuclei and showed complex configuration with back-to-back arrangement with little intervening stroma consistent with intestinal morphology [Table/Fig-2a,b]. Pyloric metaplasia was also noted at places [Table/Fig-2c]. As pyloric metaplasia was focal, differential diagnosis of pyloric gland adenoma was ruled out. No foci of invasion were seen. Sections from the adjacent areas showed papillary hyperplasia with similar morphology. Few areas showed features consistent with chronic cholecystitis. Immunohistochemical analysis was not done due to lack of facility for the same.



[Table/Fig-1]: Gross image of pale yellow, sessile, polypoidal mass, protruding into the lumen of gall bladder and measuring 1.0 cm in diameter.

As invasive carcinoma may not be detected grossly and may even occur away from Intracholecystic Papillary Neoplasm (ICPN), therefore, regrossing was done and entire gall bladder was submitted for histologic evaluation. HPE revealed similar findings and no foci of invasive carcinoma were detected. Based on gross features (papillary, intraluminal growth measuring 1 cm) and microscopic findings (compact back-to-back arrangement of glands with little intervening stroma, minimal cytologic atypia and maintained nuclear polarity), a diagnosis of ICPN with low-grade intraepithelial neoplasia was given. The postoperative course was uneventful and the patient was discharged and was under regular follow-up till the writing of the present report.



[Table/Fig-2]: a) Section show glands arranged in papillary pattern with thin fibrovascular core. (H&E stain, 40X); b) The glands arranged in papillary pattern (marked with arrow) show back-to-back arrangement with little intervening stroma and are lined by columnar epithelium with basally located nuclei (H&E stain, 100X); c) Focus showing pyloric metaplasia (marked with arrow and in inset) (H&E stain, 100X).

DISCUSSION

The incidence of mucosal polypoid lesions of the gall bladder is 5-7% in the general population [1]. ICPN is a polypoidal lesion that has been put under the category of 'Benign epithelial tumours and precursors' in the World Health Organisation (WHO) 2019 classification of the tumours of gall bladder and extrahepatic bile ducts [2]. ICPN is a papillary, intraluminal growth that arises in the mucosa of gall bladder. It is usually non invasive, but may exhibit low-grade or high-grade dysplasia. If there is a component of invasive carcinoma, the lesion is referred to as ICPN with associated invasive carcinoma. As ICPN is a rare lesion that has been described recently, hence, the diagnostic criteria are not very well defined, thus making it difficult to differentiate it from other polypoidal lesions.

Adsay V et al., described the entity in detail in 2012 after analysing 123 cholecystectomy specimens that had a well-defined exophytic neoplasm measuring ≥1 cm, followed by some case reports and two case series by Isozaki M et al., describing 23 cases and Bennett S et al., which included seven cases [3-5]. According to the study published by Adsay V et al., ICPN was found in 0.4% of cholecystectomies and in 6.4% cases, gall bladder carcinomas arise in association with ICPN [3]. In their study, the average tumour size of 2.6 cm was observed with a median of 2.2 cm (range, 1.0 to 7.7 cm); 70% of the cases were found to be solitary while 30% were multifocal. In the present case, ICPN was found in 0.6% of cholecystectomies (similar to incidence noted by Adsay V et al.,) the tumour was solitary and measured 1.0 cm. The most common locations were fundus and body (88% of the cases), similar to the index case. Adsay V et al., further observed that ICPN occurred more commonly in females, between 20-94 years (mean age 61 years); half of the patients complained of upper outer quadrant pain, and in the other half, lesion was detected incidentally and gall stones were identified in 20% of the cases [3]. In the present study, the patient did complain of upper quadrant pain but the diagnosis of ICPN was incidental upon HPE.

There are no known aetiological factors and unlike gall bladder carcinomas, ICPN has no association with gall stones [2]. It is believed that these intraepithelial neoplasms represent an "adenoma-carcinoma" sequence [3,6-8]. Although 90% of the ICPNs showed a mixture of papillary and tubular areas, 43% were categorised as papillary, 26% as tubular, and 31% as tubulo-papillary [3]. ICPN can have various cell lineages like biliary, gastric, intestinal and oncocytic as also seen in dysplastic lesions of bile duct and pancreas, the most common cell lineage being biliary, seen in 50% cases, followed by gastric pyloric in 20% cases, gastric foveolar in 16%, intestinal in 8% and oncocytic in 6% cases [3,9]. Immunohistochemical profile of these lineages reveal that 66% of biliary type were MUC1+, all cases of gastric foveolar type were MUC5AC+, 92% of gastric pyloric type were MUC6+, intestinal type were 100% CK20+; 75% CDX2+; 50%, MUC2+ while oncocytic type showed 17% positivity for HepPar and 17% for MUC6; however, in 90% cases, a secondary or unclassifiable pattern and hybrid immunophenotypes were detected [3,7,10]. Based on highest degree of cytoarchitectural atypia in the epithelium, ICPNs are classified as low-grade or high-grade. Mild-moderate atypia is seen in low-grade ICPNs while high-grade lesions reveal architectural complexity, nuclear pleomorphism and loss of polarity [2].

It has been observed that the lesions which are less than 1.0 cm in size are less likely to be associated with invasive foci, but the larger lesions showed more propensity towards neoplastic transformation through the adenoma-dysplasia-carcinoma sequence [3,6-8]. Half of the lesions measuring ≥1 cm have foci of invasive carcinoma at diagnosis [3]. Morphological features associated with the presence of invasive foci are the presence of a papillary pattern, high-grade dysplasia, and the predominance of a non pyloric cell line [8,11]. Most of the invasive carcinomas seen in ICPNs are pancreato-biliary-type gall bladder adenocarcinomas; however, other types such as mucinous, neuroendocrine, etc., are also seen [3]. Because most lesions are diagnosed after surgery and are not suspected before surgery, no specific management strategy is described. In most cases, cholecystectomy or radical cholecystectomy was performed when the suspicion of adenocarcinoma of the gall bladder was raised on the basis of the imaging studies [12]. Simple cholecystectomy without lymphadenectomy is done if ICPN is diagnosed preoperatively [8,13]. Patients with non invasive ICPNs had one, three and five years survival rates of 90%, 90%, and 78%, while those with associated invasive disease had survival rate of 69%, 60%, and 60%, respectively [3,9].

Thus, histopathological study is essential and helpful in defining the main characteristics that impact management, survival and prognosis in these patients.

CONCLUSION(S)

Intracholecystic papillary neoplasm in the gall bladder is similar to their pancreatic and biliary counterpart. They show variable morphological sub-types, a mixture of papillary or tubular growth patterns and low-grade or high-grade dysplasia, often with significant overlap. ICPNs have a relatively indolent course and better prognosis as compared to pancreato-biliary type gall bladder carcinomas. Further studies are required to define pathological features, that may help in diagnosis and determining prognosis in these cases.

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