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Case Report

A case series of intraductal papillary neoplasms of the pancreas and biliary tract: a tertiary center experience

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Abstract: Intraductal papillary neoplasms of the pancreas (IPMN) and biliary tract include the papillary neoplasms arising from the extra and intrahepatic bile ducts, gall bladder and pancreas. There are very few published reports of IPMN. In this series, we have studied clinicopathologic features of 13 patients of IPMN diagnosed in our department from January 2016 to July 2022. The gross and microscopic pathology of these tumors was reviewed including size, appearance, type of epithelial differentiation, dysplasia and presence or absence of invasive component. The cases included intraductal tumors of pancreas (4), gall bladder (3) and intra and extrahepatic biliary tract (6). The majority showed biliary type of epithelial differentiation. Invasive malignancy was seen more frequently in neoplasms of the biliary tract. IPMN patients showed aggressive behavior and mortality. The article highlights detailed gross and histopathologic examination for appropriate diagnosis of these tumors. Importance of adequate sectioning to avoid misdiagnosis of invasive carcinoma is emphasized.

Keywords: Pancreatic intraductal neoplasms, intraductal papillary mucinous neoplasm of the pancreas, biliary tract neoplasm, bile duct neoplasms, gall bladder neoplasm, pancreatic IPMN

Introduction

Ohashi et al. in 1982 described intraductal papillary mucinous neoplasm (IPMNs) as pancreatic neoplasms that accumulate mucin within dilated ducts, which he termed "mucus secreting pancreatic cancer". Throughout the early 1990s, this entity acquired many names including "mucinous ductal ectasia", "mucin hypersecreting tumor", "mucin-producing tumor", "intraductal mucin hypersecreting neoplasm" and "intraductal papillary-mucinous tumor". In 1996, the World Health Organization officially classified these tumors as a distinct histological type of exocrine tumor of the pancreas and designated intraductal papillary mucinous neoplasm (IPMN) to replace the multitude of older terms [2]. Intraductal papillary neoplasms of the pancreas and biliary tract include the papillary neoplasms arising from the extra and intrahepatic bile ducts, gall bladder and pancreas. These are grossly visible mucin-producing epithelial tumors. All these are rare neoplasms with limited literature. IPMNs of the pancreas affect predominantly men (average age 60 years) and frequently (80%) arise in the head of the pancreas. IPMNs account for approximately 3% to 5% of exocrine pancreatic neoplasms, a proportion that is rising with the increased detection of small IPMNs because of the greater use of cross-sectional imaging [3]. Intraductal papillary neoplasms of bile ducts can be very similar to those seen in the pancreas (intraductal papillary mucinous neoplasms) and generally involve extensive areas of the intrahepatic and/or the extrahepatic bile ducts with predilection for the latter. Histologically, IPMNs are composed of mucin producing columnar cells showing papillary proliferation and variable degrees of cellular atypia, even within an individual neoplasm [3]. These lesions can show dysplasia with a proportion of them also showing an invasive component. IPMNs represent one of the recognized

precursors to invasive ductal carcinomas. Imaging may not guide about the degree of dysplasia or invasion. A detailed pathologic examination is important for appropriate diagnosis. The criteria for diagnosis and classification have been updated and revised in the WHO 2022 classification. Hence the need for a complete, thorough understanding of these tumors is essential.

Case presentation

We retrospectively reviewed thirteen patients with intraductal papillary neoplasms diagnosed in our department from January 2016 to July 2022. The procedures followed were in accordance with the ethical standards of the Declaration of Helsinki 1975, as revised in 2013. The clinical, demographic, imaging and pathologic details were collected from archival medical records and patient identity was never disclosed in the entire study. This study involves retrospective analysis of data obtained from the archival medical records. There was no participation of human subjects in the study. Hence no ethical clearance was obtained. However, informed consent was taken from the patients at the time of surgical procedure.

The gross morphology of the tumors including size and appearance was noted. The tumors were extensively sectioned to avoid misdiagnosis of invasive component. The slides were reviewed and classified according to the WHO 5th Edition of GI neoplasms. The tumors were classified according to the epithelial differentiation into biliary, intestinal or gastric type. Degree of dysplasia and presence or absence of invasive component was noted. Follow up was obtained wherever available.

The study included 13 patients. The complete demographic, pathologic, radiologic details and follow up details of all the patients is provided in **Table 1**. The main presentation was pain in the abdomen. The tumor marker levels were not available. Majority (85%) of the patients underwent resection of the tumor. **Figure 1** illustrates some radiological findings seen in these tumors.

Intraductal papillary mucinous neoplasms of pancreas (IPMN, n=4, **Figures 2** and **3**): These were seen in elderly patients with mean age of 69 years. All were seen in the head of pancreas. Three were intestinal type and one was biliary type. Three cases showed dysplasia (high grade in two and low grade in one) and one was associated with invasive carcinoma. Three of the four patients expired in the early postoperative period.

Intracholecystic papillary neoplasm (ICPN, n=3, **Figure 4**): These were identified in three female patients with mean age of 55 years. Two were intestinal type and one was biliary type. Two of these tumors showed an invasive component.

Intraductal papillary neoplasm of the bile duct (IPN, n=6, **Figure 5**): This included four female and two male patients with a mean age of 57 years. Five of the tumors were biliary type and one was intestinal type. One of the cases showed high grade dysplasia and three others had an associated invasive carcinoma.

Discussion

Intraductal papillary mucinous neoplasm of the pancreas is an intraductal epithelial neoplasm of mucin producing cells, typically more than 5 mm arising in the main pancreatic duct and/or its branches [1]. These tumors are more commonly located in the head of the pancreas and are predominantly seen in elderly people.

Based on the cell differentiation pattern, they are subclassified into 3 types: gastric, intestinal and pancreaticobiliary. A two tired grading system has replaced the former three tired grading system for IPMN with dysplasia. The cases which were previously reported as IPMN with low and intermediate grade dysplasia are now categorized as low grade IPMN and those with high grade dysplasia are categorized as high grade IPMN. Oncocytic and tubulopapillary types are recognized as separate entity in the WHO 2022 edition [1].

Patients with IPMN of the pancreatic duct may have pancreatitis-like symptoms and those in the bile ducts often present with repeated episodes of acute cholangitis and obstructive jaundice [3]. However these tumours are being detected radiographically in individuals with no symptoms.

The decision-making criteria for surgical resection include size of the pancreatic duct and presence or absence of jaundice or mural nodules and location of the neoplasm. The main

Table 1. Demographic, pathologic, radiologic details and follow up details of all the patients

S n	Age/ sex	Site of tumour	Radiological findings	Type of resection	Epithelial differentiation	Diagnosis	Follow up
1	72/F	Pancreatic duct, head of pancreas.	MRCP, CT CECT: dilated MPD, atrophic pancreas, intraparenchymal calcification and debris in MPD, MPD diameter: 26 mm CECT: features suggestive of chronic calcific pancreatitis, thick enhancing septae in duct in body of pancreas showing post contrast enhancement. IPMN to be considered EUS: likely IPMN, string sign positive.	Whipple's resection Tumour size: 5 × 4.5 × 1.6 cm Grey white, friable.	Intestinal	IPMN with high grade dysplasia Adjacent pancreas: xanthogranulomatous inflammation	Expired
2	80/M	Head of pancreas.	EUS: dilated MPD in head of pancreas with a mural nodule.	Mural nodule biopsy.	Intestinal	IPMN with high grade dysplasia	Expired (surgery not done)
3	59/F	Pancreatic head.	CECT: well defined unilocular cyst in head of pancreas with peripheral calcification, Atrophic pancreas, pancreatic duct dilated with a diameter of 12 mm, Likely mucinous neoplasm of pancreas.	Whipples resection Tumour size: 14 × 10.8 × 8.6 cm Solid, cystic with mucinous and necrotic areas.	Intestinal	IPMN with an associated invasive carcinoma	No recurrence
4	65/M	Pancreatic head.	CECT ABD: Multiple cysts of varying size involving entire pancreatic parenchyma with mild enhancement of the septa suggestive of ductal dilatation. Heterogeneously enhancing solid component in head and body of pancreas.	Whipple's resection Tumour size: 4.5 × 4.5 cm Grey white and friable.	Biliary	IPMN with low grade dysplasia	Expired after 5 to 6 months of surgery
5	54/F	Intrahepatic bile duct.	CECT: small ill-defined soft tissue density at confluence of right and left hepatic ducts causing ductal dissociation, showing enhancement on post contrast. Lesion involving left hepatic ductal system, possibility of cholangiocarcinoma.	Left hepatectomy and caudate lobectomy Size of tumour: 4.2 × 2 × 2 cm. Grey white and firm.	Biliary	IPN of intrahepatic bile duct	No recurrence noted 3 months post operatively
6	46/M	Bile duct.	MRI Abdomen: Intraductal heterogenous lesion with post contrast enhancement in left duct of liver with left duct dilatation.	Left hepatectomy, hepatic duct resection and cholecystectomy Tumour size: 0.8 × 0.6 × 0.5 cm Biopsy: suggestive of IPN with microinvasive carcinoma.	Biliary	IPN with associated invasive carcinoma	No recurrence noted 7 months post operatively
7	60/F	Left hepatic duct.	CT: Ill-defined lesion at confluence of hepatic duct MRCP: lesion in hepatic hilum involving caudate lobe.	Left liver resection Tumour size: 2.2 × 1.9 × 0.5 cm Grey brown, ulceroproliferative, soft to firm.	Biliary	IPN with an associated invasive carcinoma	Lost to follow up
8	73/M	Bile duct.	-	Left lobe of liver Grey white, friable.	Biliary	IPN	Lost to follow up
9	55/F	Common bile duct.	MRCP: dilated CBD with a polypoidal filling defect in distal CBD.	Biopsy, CBD polyp Tumour size: 1 × 0.6 × 0.2 cm. Appearance: polypoidal.	Biliary	IPN with high grade dysplasia	No recurrence 5 years postoperatively
10	56/F	Intrapancreatic common bile duct.	CECT: mass lesion in distal CBD, enlarged nodes at poorly dilated CBD.	Whipples resection Tumour size: 2 × 2 × 1.5 cm Ulceroproliferative, grey white and firm.	Intestinal	IPN with associated invasive carcinoma	Lost to follow up
11	43/F	Gall bladder.	CECT abdomen: ill-defined soft tissue density lesion in gall bladder with postcontrast enhancement with irregularly thickened and enhancing wall of gall bladder. To rule out malignancy.	Radical cholecystectomy Size: 2.5 × 2 × 1 cm Grey white, polypoidal lesion.	Intestinal	ICPN with associated invasive carcinoma	Lost to follow up

12	62/F	Gall bladder.	CECT: well-distented gall bladder, irregular nodular wall thickening with enhancement and multiple calculi, features suggestive of cholelithiasis with gall bladder Neoplasm.	Radical cholecystectomy Tumour size: 6.5 × 4.3 × 3 cm Grey white to yellow, friable papillary growth CT guided FNAC: malignancy favouring adenocarcinoma.	Intestinal	ICPN with associated invasive carcinoma	-
13	61/F	Gall bladder.	CECT abdomen: Gall bladder: Cholelithiasis, enhancing polypoidal intraluminal growth along anterior wall of body of gall bladder with no demonstrable extension into peri-gall bladder fat and few calcifications, prominent CBD, which is smoothly tapering into the pancreas.	Cholecystectomy Tumour size: 1.5 × 1 × 0.5 cm Grey white, polypoidal.	Biliary	ICPN	-

Abbreviations: IPMN: intraductal papillary mucinous neoplasm of pancreas, IPN: intraductal papillary neoplasm of bile ducts, ICPN: intracholecystic papillary neoplasm, CBD: common bile duct, CT: Computed Tomography, MRCP: Magnetic Resonance Cholangiopancreatography, MRI: Magnetic Resonance Imaging, EUS: Endoscopic ultrasound, MPD: main pancreatic duct.

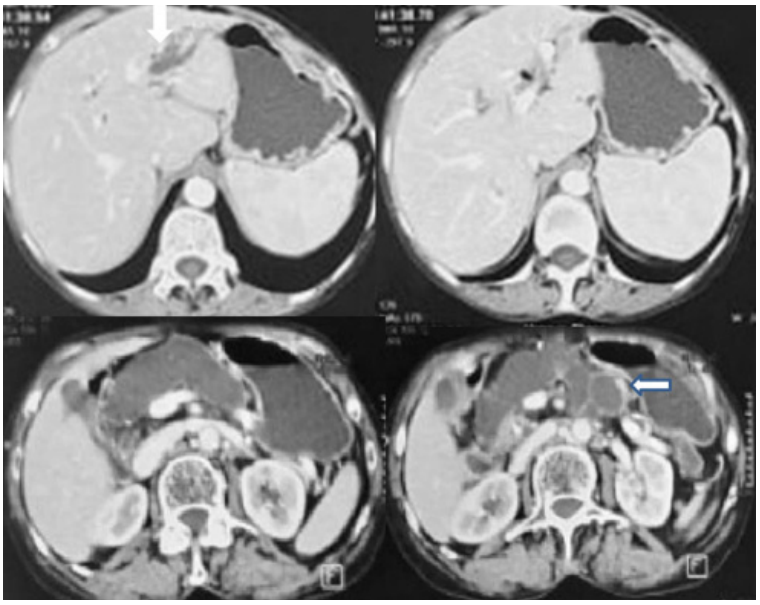

Figure 1. CT (top): dllated intrahepatic bile duct and soft tissue density lesions in left lobe of liver (white arrow). CT (bottom): dilated pancreatic duct with nodular septations (white arrow).

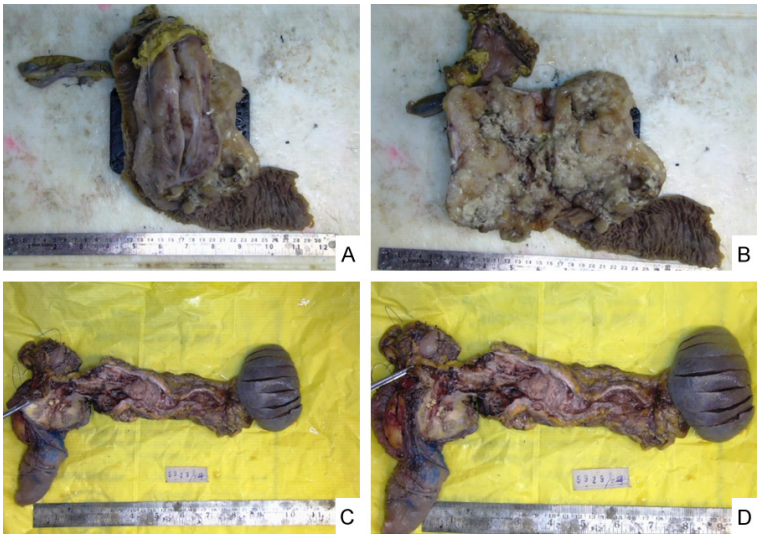

Figure 2. Gross image of intraductal papillary mucinous neoplasm showing mucinous and necrotic areas (A, B), Gross image shows dilated pancreatic duct and calcification (C, D).

duct IPMN of the pancreas requires surgery if the size is more than 10 mm, presents with jaundice or there is presence of mural nodule on imaging. In ICPN, surgical resection is indicated in patients with obstructive jaundice, mural nodule ≥ 5 mm or suspicious/positive cytology. The bile duct IPMNs should be resected unless the lesions are multifocal in which case chemotherapy and laser ablation are other options.

CEA may be elevated in case of IPMN of pancreatic duct whereas IPMN of bile ducts may have elevated bilirubin and alkaline phosphatase due to biliary obstruction [4].

In pancreatic IPMN's, prognosis also depends on the location of IPMN's as main duct IPMN's are usually high grade and associated with worse outcome compared to branch duct IPMN. Presence of invasive component carries the worst prognosis. Overall, 5-year survival in non-invasive IPMN is 75-90% and invasive IPMN is 25-50%.

L you et al. have shown that increased serum CA19-9 and CEA concentrations are independent predictors of invasive carcinoma derived from IPMN, and increased serum CA24-2 and hsCRP concentrations are significantly associated with the risk of invasiveness. Combined detection of CA19-9+CA24-2+CEA proved to be the most accurate in predicting the invasiveness of IPMN [4].

The mean age of presentation and site of tumor in our study was 69 years and the head of pancreas respectively, which were similar to age and site of the case reported by Fernandes *et al.* [5]. Three of the four cases showed intestinal morphology whereas one showed biliary morphology. Predominance of intestinal morphology was similar to Harouachi *et al.* [6].

Invasion could not be assessed in one of these cases as only mural nodule biopsy was submitted.

Harouachi et al. reported an unusual case of a 47-year-old female with a large intraperitoneal

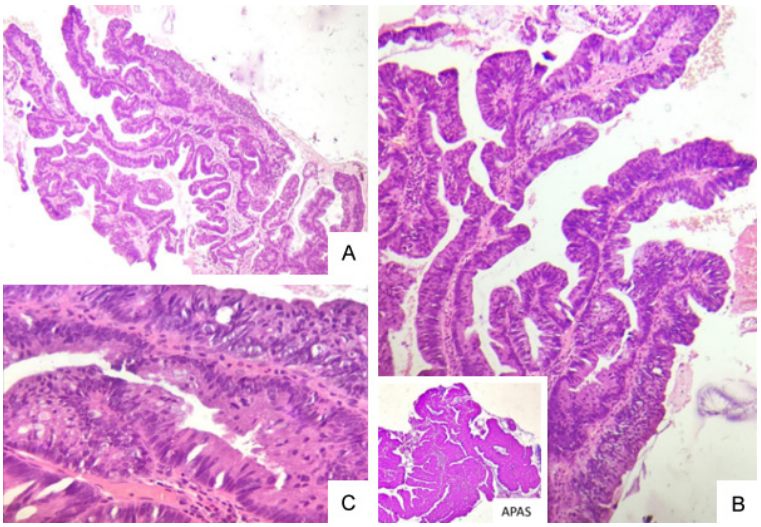

Figure 3. Intraductal papillary mucinous neoplasm with high grade dysplasia. H&E-stained sections of papillary structures lined by intestinal type epithelium with high grade dysplasia, (A-40 ×, B-400 ×, C-100 ×). Inset shows loss of apical mucin (Alcian-PAS, 100 ×).

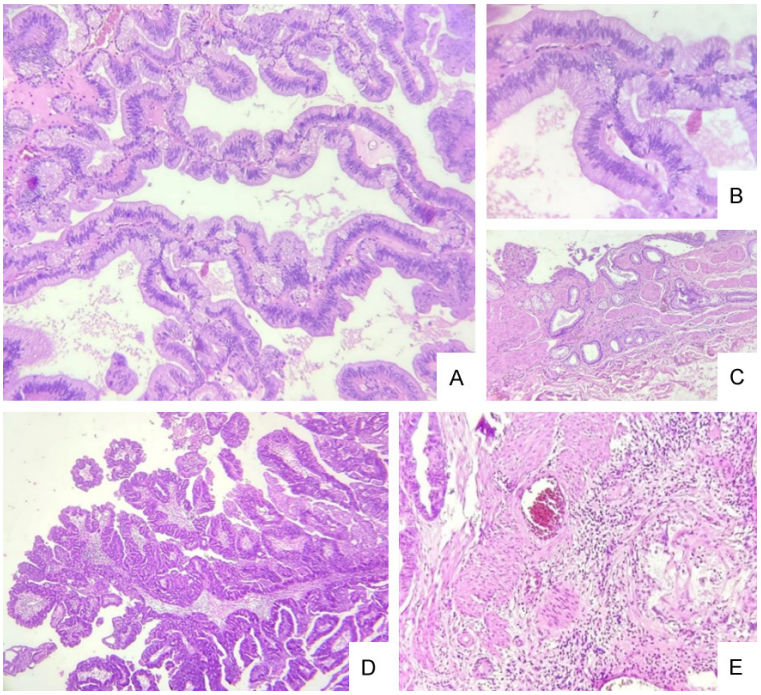

Figure 4. Intracholecystic papillary neoplasm with biliary type epithelium (A, B - H&E, A-100 ×, B-400 ×), Adjacent gall bladder (C - H&E, 100 ×), Intracholecystic papillary neoplasm with associated invasive carcinoma, intestinal type epithelium (D, E - H&E, D-40 ×, E-200 ×).

mass involving the neck and body of the pancreas measuring 18.5 × 12.8 × 19 cm [6]. This large mass on histopathological examination was reported as intraductal papillary mucinous neoplasm of intestinal type without an associated invasive component. One of the cases in our study also had a large pancreatic head mass measuring 14 × 10.8 × 8.6 cm with intestinal type of epithelium similar to the above case but was associated with invasive carcinoma.

Some of these tumors have also been reported to occur following repeated bouts of pancreatitis [6]. In our study the most common symptom was abdominal pain. Bouts of pancreatitis was not observed.

Pfluger et al. has reported the largest series of 126 cases who underwent pancreatic resection for non-invasive IPMNs [7]. They tried to evaluate risk factors for recurrence of these tumors. They concluded that family history of pancreatic cancer and high-grade tumors are associated with an increased risk of recurrence. Margin positivity was not a major criterion for recurrence but the size and grade of the dysplastic focus at the margin significantly correlated with recurrence in margin positive patients [7].

We did not identify any recurrence, however mortality of the primary pancreatic tumors was high probably due to large size of the tumors and risks associated with radical pancreatic resections. There was no correlation of tumor size with postoperative survival in our series.

Differential diagnosis of IPMN include Pancreatic intraepithelial neoplasia (PanIN), mucinous cystic neoplasms (MCN) and retention cysts. PanIN are microscopic, non-invasive, flat or papillary lesions less than 5 mm in diameter. MCN occur typically in women and are located most commonly in the tail or body of the pancreas. They do not communicate with the duct system and

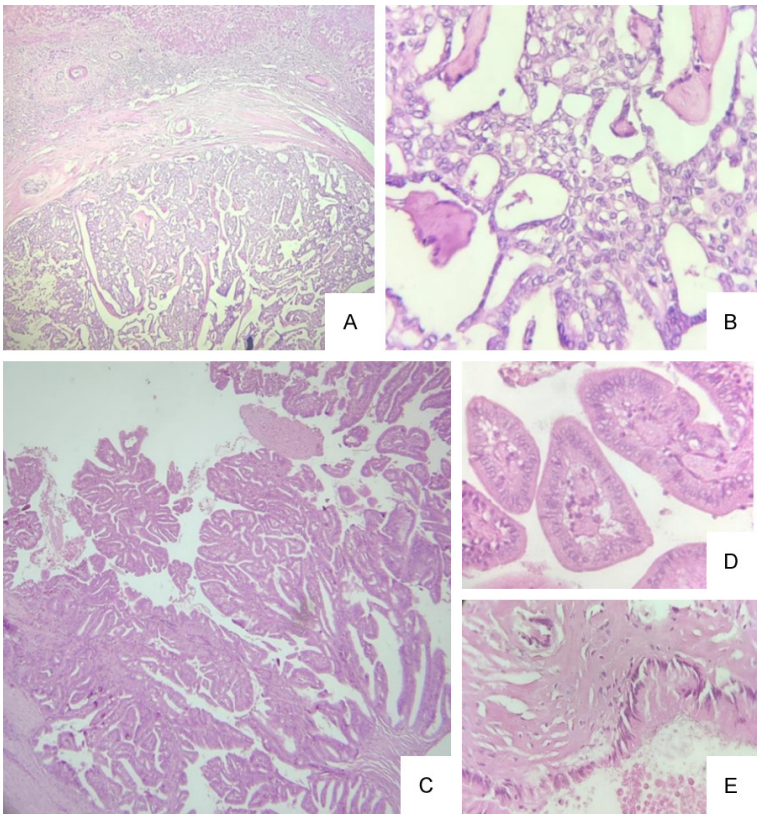

Figure 5. Intraductal papillary neoplasm of bile duct (A, B): Circumscribed lesion (A - H&E, 40 ×), Biliary type of epithelium (B - H&E, 400 ×); Intraductal papillary neoplasm with associated invasive carcinoma (C-E): Papillary lesion with biliary type epithelium (C, D - H&E, C-100 ×, D-400 ×), Focus of invasive carcinoma (E - H&E, 400 ×).

have ovarian type stroma which is positive for hormone receptors. IPMNs do not show ovarian type stroma and are intraductal neoplasms. Retention cysts are unilocular and are usually located at the periphery of a mass lesion. They are lined by a single layer of ductal epithelium without nuclear atypia. They do not show florid papillary architecture like IPMN.

Intraductal papillary neoplasm of the bile ducts (IPN) is a premalignant neoplasm with intraductal papillary or villous growth of biliary type epithelium. Median age of presentation is 50-70 years with a male predominance. These lesions can be seen in intrahepatic (Type 1) and extrahepatic bile ducts (Type 2). Intestinal, biliary, oncocytic and gastric epithelial differentiation can be seen [1]. Mean age of the patients in our series was 57 years with female predilection. Other studies reported an age range of 66-67 years and a male predilection [8, 9]. The presence of invasive carcinoma was highest in ductal tumors in our series which has not been reported in literature.

Dutta *et al.* reported a case of a 67-year-old male with intraductal papillary neoplasm of the bile duct [8]. This study concluded that this lesion is rare in the Indian population, difficult to diagnose pre-operatively but with proper surgical management these patients can have a good long-term prognosis [8]. In our study also 3 out of the 6 patients with intraductal papillary neoplasm of the bile ducts had no recurrence on follow up thus suggesting a good long-term prognosis. The other three patients were lost to follow up.

Li et al. reported two patients with IPMN of the bile duct. One patient was a 66-year-old male who complained of upper abdominal pain for 3 years [9]. Computed Tomography scan showed an interruption in the intrapancreatic common bile duct and dilation of the extrahepatic and intrahepatic bile ducts. Microscopically the intrahepatic bile duct, common bile duct and cystic duct showed an intraductal papillary neoplasm with high grade dysplasia. The other patient was a 67-year-old male who had an intraductal papillary neoplasm with low grade dysplasia with focal high-grade dysplasia. The patients were followed up for a period of 8 months and 6 months respectively with no recurrence [9]. One of our cases also had dilatation of the common bile duct (CBD) with a filling defect in the distal part on magnetic resonance cholangiopancreatography. This case was diagnosed as IPN with high grade dysplasia. On follow up three of our patients did not show recurrence.

The differential diagnosis of IPN includes micropapillary biliary intraepithelial neoplasia (BilIN), intraductal polypoidal metastasis from extrahepatic organs. Micropapillary biliary intraepithelial neoplasia occurs in the large intrahepatic bile ducts. These lesions are less than 3 mm in

height. Metastasis from a primary colorectal carcinoma is common.

Intracholecystic papillary neoplasm (ICPN) is a grossly visible non-invasive epithelial tumor arising in the mucosa and projecting into the lumen of the gall bladder. The reported mean age at presentation is 61 years with female predominance. These tumors display morphological heterogeneity [1].

The mean age in our series was 55 years and female dominance similar to that reported by Yokode et al. [10]. Biliary subtype is the most common as in the cases reported by Muranushi et al. [11]. However, in our study, intestinal morphology was predominantly seen.

ICPNs are present in less than 0.5% of gall bladders removed for chronic cholecystitis and cholelithiasis. Although 50% of patients with ICPN have an associated invasive component, the prognosis of this tumor is reported to be favorable [10, 11].

Nakanuma et al. studied 38 cases of with a mean of 75 years and predominantly gastric subtype [12]. Our patients were younger (mean age 55 years) in comparison and intestinal type was the common one. The majority of the cases in their study were not associated with invasion whereas in our study two out of the three cases were associated with invasive carcinoma.

Muranushi *et al.* reported one case of intracholecystic papillary neoplasm with low grade dysplasia with biliary type of epithelium in a 70-year-old male arising in the Rokitansky Aschoff sinuses in the background of adenomyomatous hyperplasia [11]. They concluded that it is necessary to consider the possibility of this tumor in cases with adenomyomatous hyperplasia. Two of our cases of ICPN studied did not show adenomyomatous hyperplasia but two out of the three cases had associated cholelithiasis, one case had associated chronic cholecystitis and in one of the case the entire gall bladder was involved by tumor.

Yokode *et al.* reported gastric type intracholecystic papillary neoplasm with focal oncocytic morphology associated invasive carcinoma in a 58-year-old female [10]. Our series showed intestinal and biliary epithelia.

The differential diagnosis of ICPN are biliary intraepithelial neoplasia and pyloric gland adenoma. Biliary intraepithelial neoplasia is a microscopic, noninvasive, flat or micropapillary preinvasive lesion confined to gall bladder, less than 5 mm in height. Pyloric gland adenoma is composed of densely packed pyloric gland like structures which differ from gastric type of ICPN which show foveolar and pyloric gland components [12].

Conclusion

We present a comprehensive case series of the rare intraductal papillary neoplasms of pancreas and biliary tree. Histopathology is important for accurate diagnosis, documentation of dysplasia and invasive carcinoma.

Disclosure of conflict of interest

None.

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