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Case Report

Intraductal papillary neoplasm of bile ducts: report of a case and literature review

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ABSTRACT

A 67 year old male with right upper quadrant abdominal pain diagnosed with intraductal papillary neoplasm of bile ducts (IPNB) by endoscopic biopsy. The patient was treated surgically and disease free on first year follow-up. Intraductal papillary neoplasm of bile duct (IPNB) is a rare entity with malignant counterparts and recently classified by The World Health Organization. The aim of this study is to present a case of IPNB and review the literature. Pubmed/MEDLINE was searched and articles were extracted. Twenty four case reports and 17 retrospective case series were evaluated. From 41 studies, 824 cases were included. There was slight male predominancy among patients and almost all cases were from eastern countries. Even though the etiology remains unclear, hepatolithiasis was the most common potential etiological association. Most cases were treated with surgical intervention. More than half of the 577 resected specimens had invasive component. Incidence rate of histopathological subtypes were as fallowed: Intestinal (35%), pancreaticobiliary (32%), gastric (19%) and oncocytic (12%). Intraductal papillary neoplasm of bile duct has an increased malignancy rates at postoperative pathological diagnosis, consequently early surgical management is important.

Keywords: Biliary, Biliary tumours, IPNB, Mucinous adenocarcinoma

INTRODUCTION

Intraductal papillary neopasm of the bile ducts (IPNB) is a rare tumor and has classified as one of the mucin-producing tumours of biliary tree by The World Health Organization (WHO).[1] IPNB cases are generally reported from eastern countries where hepatolithiasis and clonorchiasis are commonly seen.[2] Despite this knowledge, sporadic cases from western countries, without these forementioned predisposition factors, are increasingly being reported. Hepatolithiasis, clonorchiasis and primary sclerosing cholangitis are among the risk factors for developing IPNB.[3]

The clinical manifestations of IPNB are right upper quadrant pain, jauindice or cholangitis.[2-7] Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used diagnostic studies. Although they are insufficent to make a specific diagnosis, secondary findings caused by obstruction could be revealed by those methods. IPNB cases show wide range of histological characteristic and pathological features.[8] It can be classified as non-invasive and invasive diseases, and those two categories vary between low grade dysplasia and carcinoma. Phenotypes of IPNB are pancreaticobiliary, gastric, intestinal and oncocytic, similiar to intraductal papillary muscinous neoplasm of pancreas (IPMN-P). For years IPNB has been considered as biliary IPMN-P with pancreatic counterparts but some studies reported IPNB is a more aggresive tumor than IPMN-P.[9]

We herein report a case of IPNB and also conduct a literarute review to have a better understanding about histopathological features, clinical approaches and prognosis of IPNB.

CASE REPORT

A 67 year old male presented to our hospital with right upper quadrant abdominal pain without any other complaints. Patient had history for cancer of descending colon and underwent surgery for left hemicolectomy five years ago and received 8 cycles of chemotherapy treatment and has been disease free since then. He also has high blood pressure and type II diabetes.

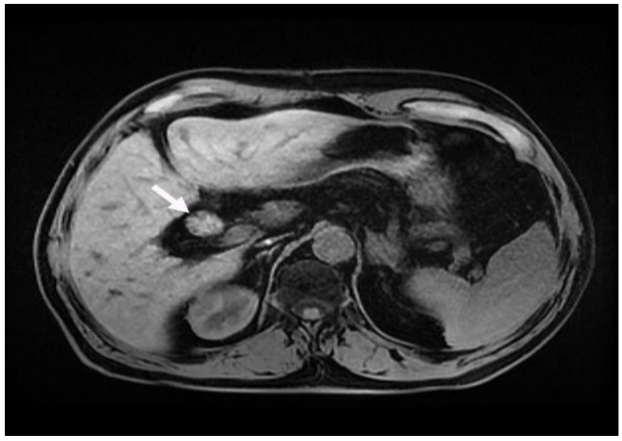

Figure 1: Axial T1W pre-contrast image. Lesion (23×19 mm) in CHD leading dilatation of intrahepatic bile ducts with high signal due to mucin content.

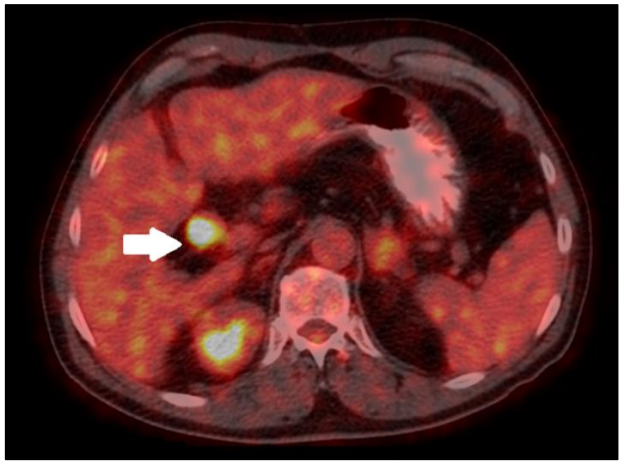

Figure 2: PET/SCAN image.

At presentation, his full biochemistry work-up and hemogram were normal but Ca 19-9 level was 40.97 U/mL (referance range: <37 UmL). Serology was negative for hepatitis A,B and C infection. Magnetic Resonance Cholangiography revealed a dilated common hepatic duct (CHD) up to 2 cm and hypodense lesions in CHD were identidfied. Common bile duct (CBD) was observed dilated and MRI showed contrast enhancing lesion with high signal due to mucin content on T1-weighted and intermediate signal on T2W-weighted sections with intrahepatic bile ducts dilatation (Figure 1).

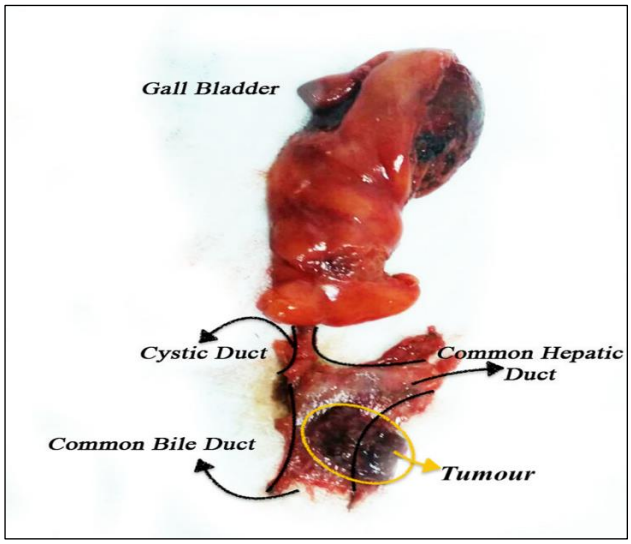

Figure 3: Location of the tumour.

PET/SCAN revealed a mass in CHD with a maxiumum standardized uptake value (SUV max) of 11.9 (Figure 2). The patient underwent Endoscopic Retrograde Cholangiopancretogram (ERCP) and CHD was dilated and irregular. Also membranous-like tissues were seen and a biopsy was obtained. Pathologic evaluation have been identified as intraductal papillary muscinous neoplasm of bile duct. He underwent surgery for segmental resection of common hepatic and bile duct with cholecystectomy and hepaticojejunostomy. The location of the tumor was junction of the CHD and CBD (Figure 3). Microscopic examination of the biliary mass was consistent with biliary intraductal papillary neoplasm. The specimen showed gastric differentiation and low-intermediate grade displasia. There was no evidence of infiltrative features. By immuno-histochemistery, the tumor was positive for mucin core protein 6 (MUC 6) and CK7 (cytokeratin); negative for DPC 4, CK 20 and CDX2. Genetic analysis was positive for G12 R mutation at KRAS gene. The resection margin was negative for tumor. The patient was discharged on eighth day after surgery and did not receive any further treatment. His one year follow up were completed with no sign of recurrence. His scans are clear and Ca 19.9 dropped to normal levels.

Preferred reporting items for systematic review and meta-analyses (PRISMA) guidelines were used to build the conduct of this study.[10] Pubmed/MEDLINE were searched on January 29, 2017 by one author to distinguish the studies according to their relevancies without using a time interval. “Intraductal papillary muscinous neoplasm AND bile ducts” and “intraductal papillary muscinous neoplasm AND biliary” were used as phrases to implement a more specific search. Studies, that were

documented as biliary muscinous neoplasms or adenocarcinoma, were included. Studies without pathology report that demonstrates IPNB or diagnosed by imaging only and duplicate studies were excluded. After the elimination of duplicate studies, 395 articles out of 531 were extracted from database system and evaluated. Articles that met the inclusion criteria were examined in full text.

DISCUSSION

Article selection after examining the studies is demonstrated in PRISMA study flow (Figure 4). There was also significant number of patients without any symptoms (10%). Possible etiological factors were identified in 231 patients from 12 studies and heaptolithiasis (80%) were the most frequent reported condition. Colonorchis sinensis (7%) and schistosomiasis (2%) are two infections mostly reported from eastern countries where it is endemic. Viral hepatitis were present in 18 (%8) individual. Tumor markers were evaluated in 75 patients from 9 studies and the percentage elevated CA 19-9 and CEA levels were 49% and 51%, respectively. ERCP, CT and MRI are the most frequent disgnostic imaging methods. Intraductal mass accompanied by bile duct dilatation on on cross-sectional imaging and mucin presence are the two most common findings. Most cases were managed surgically and the type of surgery varied according to location of the tumor.

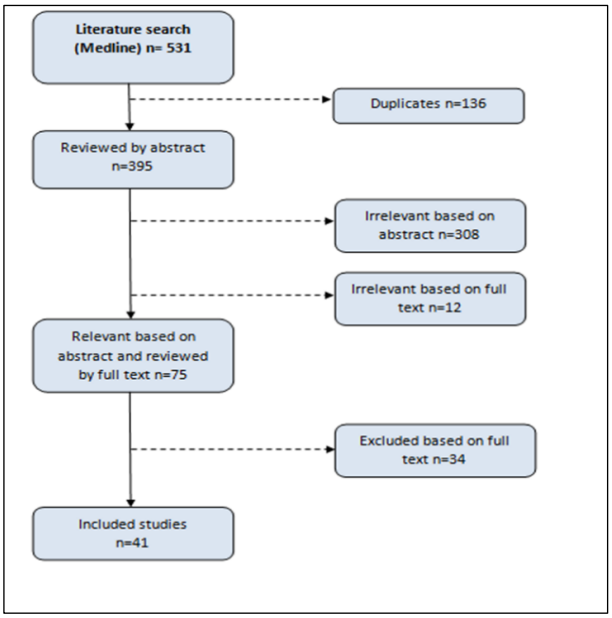

Figure 4: Study flow.

Table 1: Demographic and clinical features.

	No. of patients (%)	Total patients	References
Sex			
Male	463 (56)	824	4, 5, 7, 8, 9,12, 14, 16, 19, 21-51
Female	323 (39)		
N/A	38 (4)		
Nationality			
Asian	799 (97)	824	4, 5, 7, 8 ,9 ,12, 14, 16, 19, 21-51
Non-Asian	25 (3)		
Presentation			
Abdominal pain (RUQ)	168 (39)	429	4, 5, 7, 14, 16, 19, 21-37, 39, 44-46, 48-51
Jauindice	106 (24)		
Cholangitis	58 (13)		
No symptoms	47 (10)		
Weight loss	23 (5)		
Fever	18 (4)		
Pruritus	4 (0.9)		
Dark colored urine	3 (0.6)		
Acholic stool	2 (0.5)		
Possible etiological association			
Hepatolithiasis	187 (80)	231	7, 8, 9,14, 22, 23, 39, 40, 45, 46, 48, 51
Colonorchis sinensis	17 (7)		
Viral enfection (HBV/HCV/HBV+HCV)	18 (8/3/2) (8)		
Schistosomiasis	9 (2)		
Tumor markers			
Elevated CA 19.9	37 (49)	75	7, 14,16, 23, 25, 27, 34, 36, 43
Elevated CEA	38 (51)		

Continued.

	No. of patients (%)	Total patients	References
Diagnostic imaging			
ERCP	136 (33)	409	8,4,16,14,12,7,21, 22,23, 24, 25, 26, 19, 27, 28,29, 30, 31, 32, 33, 34, 35, 36, 37, 45, 46, 48, 49, 50
CT	118 (28)		
MRI	110 (26)		
USG	44 (10)		
EUS	1 (0.2)		
Imaging findings			
Intraductal mass	125 (42)	292	4,16,14,12,7,21,34,37,45,46,48,50
Mucin prensence at ERCP	88 (30)		
Bile duct dilation	42 (14)		
Other	37 (13)		
Treatment			
Hepatectomy	394 (74)	527	4,5,16,14,7,21,22,23,24,25,26,27, 28,29,30,31,32,33,35,36,39,44,48, 50,51
Extrahepatic bile duct exicion	98 (18)		
Pancreaticoduodenectomy	25 (4)		
Palliative intervention	5 (0.9)		
Liver transplantation	3 (0.5)		
Chemotherapy	2 (0.3)		

Table 2: Histopathologic and immunohistochemistry features.

	No. of patients (%)	Total patients	References
Tumor location			
Intrahepatic	357 (68)	520	8,9,4,5,14,7,32,41,43,45,51
Extrahepatic	139 (26)		
Intra and extrahepatic	24 (4)		
Tumor grade			
Adenocarcinoma	321 (55)	577	8,9,4,5,16,12,7,21,22,23,25,26,28,29,30,31,32,33,34,35,35, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 50
Dysplasia	246 (42)		
Low-Modorate	83 (14)		
High	86 (15)		
N/A	77 (13)		
Carcinoma in situ	26 (4)		
Adenoma	4 (0.6)		
Intraluminal mucin presence	219 (100)	219	5,12,7,21,22,24,25,26,19,27,28,29,30,31, 32,33,34,35,36,37,39,40,43,49,50,51
Histologic subtype			
Intestinal	202 (35)	574	8,5,16,12,22,26,34,37,38,39,40,43, 44,45,46,47,48,51
Pancreaticobilier	189 (32)		
Gastric	111 (19)		
Oncocytic	72 (12)		
Tumor antigens			
MUC1 (+/-)	101/7 (93/7)	108	5,12,7,22,26,28,29,3435,36,37,38,40,41,42,43,47,48
MUC2 (+/-)	69/7 (90/10)	76	
MUC5Ac (+/-)	113/1 (99/1)	114	
MUC6 (+/-)	48/0 (100/0)	48	
CDX2 (+/-)	35/5 (87/13)	40	
CK1(+/-)	1/0 (100/0)	1	
CK7 (+/-)	65/11 (85/15)	76	
CK20 (+/-)	27/6 (81/19)	33	

Histopathological features are revealed in Table 2. Tumor location in the biliary tree was identified in 520 patients and intrahepatic type was the most common (68%). Tumor grade was reported in 577 patients and 55% of the cases comprise invasive component. Histological subtype was documented in 574 cases from 18 studies. Rate of

incidance according to histopathological subtypes were as fallowed: intestinal (35%), pancreaticobiliary(32%), gastric (19%) and oncocytic (12%). Tumor antigens were assessed in 496 specimens from 18 studies and the results are revealed in Table 2.

Patients with IPNB are usually in the sixth decade of life and male predominance has been noticed among studies.[2,5,11] Most common clinical symptom is right upper quadrant pain (35-88 %) and second most common symptom is obstructive jaundice (20-36 %).[2-7] Some patients may present with acute cholangitis (5-59 %).[2]

IPNB lesions are soft, friable and mucin hypersecreting tumor and arises from both extra and intrahepatic bile duct. There are also tubuler components with or without connective tissue.[12] IPNBs are accepted as preinvasive intraepithelial neoplasm for tubular or mucinous adenocarcinoma.[12] They have tendency to grow in extrahepatic bile ducts more commonly than intrahepatic bile ducts with the ratio of 2:1.[11] Some authors suggested that biliary and pancreatic intraductal papillay neoplasms develop through the similar pathogenetic factors since they both are originated from the ventral endoderm of the foregut.[12,13] But, since the IPNB shows association with invasive disease more fruquently than IPMN-P, there are probably different oncological pathways between those two conditions. Intrahepatic IPNBs are more similar to IPMN than the extrahepatic type histopathologically.[12] In a study published by Wang et al with 19 cases, 10 out of 19 tumor showed mucin secretion [14]. The frequency of phenotypes in IPNBs are pancreaticobiliary (45%), gastric (25%), intestinal (20%) and oncocytic (10%), respectively.[5,12] Immunohistochemical study of specimens indicates that IPNB cells contain a biliary phenotype. Subtyping of IPNBs with immunostain is important to predict the prognosis of patients. MUC1/2/5AC/6, CK7 and CK20 are most frequently used markers. MUC 1 expression is usually associated with invasive lesions and especially tubuler adenocarsinoma when MUC2 over expression is related to muscinous adenocarcinoma with MUC1 negativity. [2,8] Rocha et al. showed in their study that MUC1 expression is more likely to related with pancreaticobiliary type and they also associated this anomaly with poor prognosis.[5] Molecular pathogenesis of IPNB is stil unclear but some studies showed KRAS activation and p53 mutation.[4,15,16] In our case there was also G12 positivitiy at KRAS gene.

Gordon Weeks et al published a systematic review involving 57 studies which showed 43% invasive component of 476 IPNB cases.[6] Again in two series with 19 and 32 cases showed almost 50% malignancy with IPNB.[14] Zen et al indicates in their study that IPNB is a more aggressive tumor than IPMN-P and the prognosis of patients with invasive IPNB is poorer than IPMN-P.[9]

Focal dilatation of extra or intrahepatic biliary tree, intraductal masses and growth pattern through the interior wall are considered as a warning to suspect from IPNB. Ultrasound and CT/MRI are useful imaging methods for detecting IPNB but extra attention should be paid for the patients without a visible tumor.[6] Clinically and radiologically, it is difficult to diagnose IPNB. Even though some patients had no detected intraductal masses, after resection they had been diagnosed with benign or malignant IPNB.[4] In a study, Egri et al invastigated five different cases based on their imaging features. In those cases ERCP showed filling defect and ductal dilatation and MRI show solid components of the masses.[3] Hong et al. examined MRI findings of 38 patients in their study and found that some patients manifests a thread sign (intraductal linear or curvilinear hypointense striations) on MRI which is an indicator of intraductal mucin bundles and highly specific finding for IPNB.[17] The results of F-18 FDG PET/CT scan findings are limited in literature. Contrary to carcinomas with an high activity of glucose metabolism, malignant IPNBs with small mural nodule with excessive amount of mucin may present with false negativity since mucin is insufficient with glucose intake.[18] Since endoscopic biopsy is a poor diagnostic test, early surgical management of IPNB is highly important to gain a better prognosis. Gomez et al reported a case of IPNB treated with chemotherapy with excellent results.[19]

Clinical suspicion supported by radiological and laboratory findings are very important for early treatment of this disease. Given the poor diagnostic features of ERCP with IPNB, it is useful to decompress the biliary tract with patients that present with obstructive jaundice.[6] Mucin secretion especially seen on ERCP is a possible indicator for IPNB. Paik et al investigated 25 patient who underwent surgery for biliary tumors and diagnosed with IPNB. After the pathological examination of the resection specimen, 19 cases had invasive disease when eight of them had benign features.[4] In the study of Rocha et al. with 39 cases; R0 resection, presence, depth (≥5 mm, <5 mm) and percentage (≥10%, <10%) of invasive component were associated with survival. MUC1 expression and CEA positivity are also associated with poor prognosis.[5,6] According to comparative study by Wang et al., there are similarities and differences between IPNB and IPNM-P. They speculates that being originated from the same embriological structure constitutes their similarities, whereas phenotypic subtypes (pancreatico-biliary, gastric, intestinal and oncocytic) designates their differences.[7]

Patients with a prediagnosis of IPNB should be considered as a candidate for resection, because even if the lesion is thought to be premalignant or benign it is hard to make a definite pathological diagnosis preoperatively due to incompetency of biopsy to show the degree of cytologic atypia.[20] In our case preoperative reported pathology was intraductal papillary muscinous neoplasm without showing any sign of dysplasia. But after resection, final pathological diagnosis was consisted with intraductal papillary neoplasm accompanied by low grade dysplasia.

CONCLUSION

In summary, we conclude that IPNB has wide spectrum of pathological findings. Since the pathological features and phenotypes play an important role on prognosis, making an accurate diagnosis determines course of the disease. Resection with adequate oncological margins should be performed due to high malignancy rates and its positive effect on survival.

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