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Intraductal papillary neoplasm of extra hepatic biliary tract with an associated early invasive adenocarcinoma

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ABSTRACT

Introduction: Intraductal papillary neoplasm of the bile duct (IPNB) is a pre malignant lesion, which can develop into a adenocarcinoma. If treated early, at the non-invasive stage, it has an excellent prognosis compared to cholangiocarcinoma. Case Report: A 61-year-old lady presented with intermittent episodes of fever with chills and rigors, loss of appetite, pruritus, tea colored urine, and pale sticky stools for 2 years duration. After work up she underwent a left hemihepatectomy with resection of caudate lobe and extrahepatic biliary duct with lymph node clearance. Histology revealed an intraductal papillary lesion with no mucin production, expanding the common hepatic duct and the left hepatic duct, invading the subepithelial connective tissue at a focus near the distal end of the left hepatic duct. The tumor was qualified as an intraductal papillary neoplasia of pancreatobiliary type involving the extrahepatic bile duct with associated early invasive adenocarcinoma. She required no further adjuvant treatment and is disease free for one year on regular follow up. Conclusion: The objective of this article is to emphasize the necessity of early diagnosis and aggressive and complete surgical resection to achieve maximum patient survival in this curable disease.

KEYWORDS

Extra hepatic intraductal papillary neoplasm, biliary papillomatosis, biliary pre malignant lesion
INTRODUCTION

Intraductal papillary neoplasm of the biliary tract (IPNB) is considered a precursor lesion for the development and progression of both intrahepatic and extrahepatic bile duct adenocarcinoma. These papillary neoplasms are characterized by dilated and expanded bile ducts filled with a non invasive papillary growth. The papillae are composed of proliferating biliary epithelium covering delicate fibro vascular stalks. Four phenotypes of epithelium are recognized and include pancreaticobiliary, intestinal, oncocytic and gastric types. Invasive adenocarcinoma may occur in association with intraductal papillary neoplasms. The prognosis is excellent if an IPNB is localized and non invasive, where the tumor can be completely resected. Once invasive carcinoma develops the prognosis becomes remarkably poor [1].

The available literature on this rare neoplasm is limited; therefore, the clinical course, radiological and pathologic findings, and prognosis of this neoplasm are not well understood. Though the frequencies of reports are increasing, data from South Asian context is sparse. We report a case of intraductal papillary neoplasm of extra hepatic biliary tract with evidence of an associated early invasive adenocarcinoma to emphasize the importance of precise diagnosis at an early stage and early surgical resection.

CASE REPORT

A 61-year-old lady had presented to the primary care clinic with episodes of epigastric pain radiating to back for two years duration. She has had episodes of fever with chills and rigors, loss of appetite, pruritus, tea colored urine, and pale sticky stools. These episodes developed at least once in every three months. She never had jaundice in association with these symptoms. The ultrasound scan of the abdomen revealed dilated intrahepatic ducts with no visible calculi. The patient was referred to specialized hepatobiliary clinic for further management.

The contrast enhanced abdominal computed tomography (CT) was done and it was more in favour of an intraductal cholangiocarcinoma involving left and right hepatic ducts, common hepatic duct and proximal segment of common bile duct (Bismuth type iv) with regional nodal metastasis. A magnetic resonance cholangiopancreatography (MRCP) delineated a mildly enhancing soft tissue mass involving the proximal right and left hepatic ducts, common hepatic duct and proximal common supra pancreatic biliary duct causing mild dilatation of the bilateral intrahepatic biliary radicles suggestive of cholangiocarcinoma with a normal liver (Figure 1).

The laboratory test results included; CA 19.9 13.4 u/mL (0-5 u/mL), AST 86 IU/L (10-35 IU), ALT 88 IU/L (10-40 IU/L), ALP 2043 IU/L (100-360 IU/L), total bilirubin 3.6 mg/dL (<1 mg/dL), serum creatinine 0.6 mg/dL (0.9-1.3 mg/dL), serum amylase 270 units (30-110 units), hemoglobin 11.2 g/dL (11-18 g/dL), white blood cell 8 x10⁶ (4.5–10.5 x10⁶).

The clinical details and the investigations were discussed at the Hepatobiliary multi-disciplinary team (MDT) meeting. A 10Fr X 12 cm end biliary stent was placed following endoscopic retrograde cholangiopancreatography (ERCP). Patient had four cycles of radio frequency ablations (RFA) as the lesion was deemed unresectable on CT and MRCP. One month later the previous sphincterotomy was extended and a cholangioscopy was performed to assess the progression of disease and the effect of RFA. Cholangioscopy and biopsy from the mass was non-diagnostic and yielded fibrous stromal tissue only. As the symptoms recurred, a repeat ERCP was performed and it revealed sparing of
right hepatic duct (Bismuth 111 b). Right hepatic artery and right branch of the portal vein were assessed by a CT angiogram/venogram and was found to be not involved. Patient was reevaluated at the MDT and was offered surgery to exclude a hilar cholangio carcinoma. The patient underwent left hemihepatectomy with resection of caudate lobe and extrahepatic biliary duct with lymph node clearance. A Roux-en-Y hepaticojejunostomy was performed to reconstruct the right hepatic duct. She had an uneventful recovery and was discharged on the seventh postoperative day.

The resected specimen consisted of left lobe of the liver, gall bladder and extra hepatic biliary tree including left hepatic duct, common hepatic duct, cystic duct and proximal common bile duct. The cut opened biliary duct system revealed no definite growths but a mucosal irregularity only. The gall bladder and the liver tissue were unremarkable with no evidence of lithiasis.

The entire extrahepatic biliary tree was examined microscopically and this showed a multifocal intraductal papillary lesion, expanding the left hepatic duct and the common hepatic duct, composed of arborizing papillae lined by moderately pleomorphic cells of pancreaticobiliary differentiation (figure 2 and 3). There was no mucin production. This intraductal tumor was invading the subepithelial connective tissue at a focus near the distal end of left hepatic duct (figure 4). The invasive component was composed of irregular acinar structures infiltrating through the desmoplastic stroma. No perineural or vascular invasion was identified. No intrahepatic ductal component was identified. The hepatic parenchyma showed mild to moderate steatosis. The portal tracts showed extensive bile ductular reaction and moderate inflammatory infiltrate in keeping with the morphological changes of large bile duct obstruction. The gall bladder showed no lithiasis or epithelial dysplasia. Thus this tumor was qualified as an intraductal papillary neoplasm associated with early invasive adenocarcinoma-pancreaticobiliary type (PT1a N0 Mx).

She did not receive further adjuvant treatment but was enrolled for follow up which is planned at regular intervals via clinical examination and biochemical investigations (liver profile. CA 19.9). Radiological investigations will be considered if a need arises.

DISCUSSION

Pre malignant biliary and pancreatic lesions are rare disorders [2]. The recent WHO classification of tumors of the gall bladder and extra hepatic bile ducts proposed two precursor lesions for the development and progression of extrahepatic biliary carcinoma namely biliary intraepithelial neoplasia (BilIN) and intraductal papillary neoplasms (IPNB) [1].

IPNB is the clinicopathological condition which was previously referred to as biliary papillomatosis [1]. IPNB/ biliary papillomatosis is characterized by intraductal papillary proliferation of atypical biliary epithelium over a delicate fibro vascular stalks that may involve extensive areas of the extrahepatic bile ducts and even extend into the gall bladder and intrahepatic bile ducts. Four phenotypes of epithelium are recognized and include pancreaticobiliary which is the commonest type of epithelium identified in IPNB, intestinal, oncocytic and gastric. The lining cells are cuboidal or columnar and may contain variable amount of cytoplasmic and extracellular mucin. The nuclei are round to ovoid or elongated and contains small nucleoli [3]. Cytological atypia and mitoses are uncommon although obvious carcinomatous changes can be identified in some cases [4, 5].

Despite its rarity IPNB/ biliary papillomatosis has been extensively discussed in the literature because of its characteristic clinical presentation and proven malignant potential [4]. These
intraductal tumors with frond like papillary projections are friable and slough easily giving rise to fragments of floating tumor within the bile ducts. This could give rise to intermittent and partial biliary obstruction and this could mimic biliary stone disease clinically and radiologically [6, 7]. Our patient had episodic symptoms of acute cholangitis and biliary obstruction for two years duration which would most likely due to intermittent sloughing off of the tumor into the duct system.

In the previous edition of WHO classification of tumors of the gall bladder and extrahepatic bile ducts, biliary papillomatosis was considered as a benign entity with a variable malignant potential [8]. The current edition includes papillomatosis under the novel entity of IPNB and classify it as a premalignant lesion [1]. IPNB could have low, intermediate or high grade intraepithelial neoplasia. Some of these intraductal papillary lesions could invade the beyond the wall of the bile duct to cause an invasive carcinoma like in our patient. Once invasive carcinoma develops prognosis is related to the stage of the invasive component and other conventional prognostic factors. The prognosis is excellent if an IPNB is localized and non-invasive, where the tumor can be completely resected. Wide distribution and invasion raises the potential for metastasis, causes surgical eradication difficult hence a poor prognosis. Perineural invasion and lymphatic permeation are common and are significant prognostic indicators [1].

IPNB may evolve through a common pathological process and shares clinicopathological features with pancreatic neoplasms such as intraductal papillary mucinous neoplasm of the pancreas (IPMN-P) [9,10]. It is well established that intraepithelial pancreatic neoplasia is the microscopic precursor of pancreatic carcinoma and IPMN-P or mucinous cystic neoplasms are the macroscopic precursor lesions [11, 12]. In bile duct carcinomas on the other hand BilIN or IPNB are thought to be similar precursor lesions and molecular characteristics of these in regard to carcinogenesis have been clarified [13]. Therefore IPNB seems to be a counterpart of IPMN-P. Occasional association with mucin hypersecretion is one of the histological similarities between IPNB and IPMN-P, although the degree of extracellular mucin production may not always be extensive as that found in most pancreatic IPMN [14]. A study done by Ohtsuka M et al.. concluded that IPNB with mucin secretion showed striking similarities to IPMNP, but IPNB without mucin secretion contained of a heterogeneous disease group [15].

Tadashi Terada [16] has presented 6 cases and Albores-Saavedra et al.. [17] has reported nine cases of non-invasive and minimally invasive papillary carcinomas of the extrahepatic bile duct. Their cases of intraductal papillary carcinomas of extrahepatic bile duct has not shown macroscopic and microscopic mucous hyper secretion [16, 17], as seen with this case. Therefore, the above group can be considered as different from intraductal papillary-mucinous neoplasm of the bile ducts, a suspected biliary counterpart of pancreatic intraductal papillary-mucinous neoplasm [18, 19].

Though early detection, early treatment are important in the treatment of bile duct cancer, it is necessary to sub classify it according to the clinicopathological characteristics. They are subdivided into pancreateobiliary, intestinal, gastric, or oncocytic based on morphology of the cells forming the lesion [20]. IPNBs can be also classified morphologically into polypoid, cast-like growth, superficial-spreadling, and cystic type [21]. However no correlation has been demonstrated between these features and the tendency for invasive cholangiocarcinoma or survival rates [1, 22, 23, 24].

A study done in 2008 pointed out that 20% of IPNB were incidentally identified [25]. This disease has equal distribution among males and females. The commonest age group affected is between 50-70 [1].
Place of CT scan for revealing intraductal lesions has been found to be nonspecific and variable. 92% showed bile duct dilatation with or without an intraductal mass and cystic change of bile duct [25]. When intraductal masses or nodules are seen with localized dilatation of the intrahepatic bile duct on CT, malignant papillary tumor of the intrahepatic bile duct should be included in the differential diagnosis [24].

The treatment of choice for IPNB is aggressive surgical resection [25]. But there are few rare reported cases of IPNB, managed long term using endoscopic procedures such as endoscopic retrograde biliary drainage, endoscopic biliary sphincterotomy and papillary balloon dilatation [26]. But According to Yeh et al. fifty nine out of hundred and twenty nine (forty six percent) IPNB cases had progressed to invasive carcinomas at the time of diagnosis [27]. As this can be considered relatively a high proportion, the need for early diagnosis and excision is recommended. Once invasive carcinoma develops, prognosis is related to the stage of the invasive component and other conventional prognostic factors [1]. Some of the reports have revealed the prognosis in patients with lymph node metastasis as very poor [27]. In addition, several reports have suggested excellent prognosis of IPNB over cholangiocarcinoma with minimal recurrence rate [15, 16, 25]. One study has indicated The median survival time of resected patients as 59.8 months and 1-, 2-, and 4-year survival rates as 90.5%, 84.0%, and 84.0%, respectively [25].

Considering the above factors as well as the difficulty of surgical excision in the hilar region and aggressive behavior of widely distributed disease, the possibility of early surgical resection with the curative intent should be always sought.

CONCLUSION

In this case the major component of the lesion is the intraductal papillary neoplasm, which is considered a pre-malignant lesion with good prognosis. However as there is a focus of invasion qualifying this tumor as intraductal papillary neoplasm with associated adenocarcinoma the prognosis is worse than that of a pure intra ductal lesion. Considering the malignant potential of IPNB which was well demonstrated in our case and the poor prognosis of hilar cholangiocarcinomas these premalignant lesions merits early diagnosis and complete surgical resection to obtain best prognostic benefits.

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Figure 1: Magnetic resonance cholangiopancreatography showing a mildly enhancing soft tissue mass involving the proximal right and left hepatic ducts, common hepatic duct and proximal common supra pancreatic bile duct causing mild dilatation of the bilateral intra hepatic biliary radicles.
Figure 2: Intra ductal complex papillary lesion within the left hepatic duct (H&E stain, x400).

Figure 3: These papillae are lined by tall columnar cells that resemble pancreatico biliary type epithelium. The nuclei show moderate pleomorphism (H&E stain, x200)
Figure 4: This intra ductal tumor invades the sub epithelial connective tissue in a focus near the origin of the left hepatic duct (H&E stain, x200).