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Large duct intrahepatic cholangiocarcinoma arising from intraductal papillary neoplasm of bile duct: A rare case report

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ABSTRACT

Intrahepatic cholangiocarcinoma (iCCA) is one of the primary carcinomas of the bile duct. It is a malignant intrahepatic epithelial neoplasm with biliary differentiation arising in the liver periphery/proximal to the left and right hepatic ducts with greater significance and more clinical and therapeutic challenges. The average age at diagnosis is >50. It presents as three major macroscopic growth patterns (mass-forming (MF), periductal infiltrative (PI) and intraductal growth (IG)). The worrisome mortality of these tumours, which accounts for 2% of all cancer-related fatalities globally each year, is caused by their discrete form, high aggressiveness and resistance to chemotherapy. Histological confirmation is necessary because the non-invasive methods currently used to diagnose cholangiocarcinoma are insufficient. We present a case of large duct intrahepatic cholangiocarcinoma of mass forming type arising from IPNB (intraductal papillary neoplasm of bile duct) with high grade dysplasia in a 60-year-old male.

Keywords: Intrahepatic cholangiocarcinoma, iCCA, Intraductal papillary neoplasm, Bile duct, Intrahepatic epithelial neoplasm.

1. INTRODUCTION

Cholangiocarcinoma (CCA) represents a diverse group of malignancies that emerge in the biliary tree. The Union for International Cancer Control (UICC) and WHO (Walter et al., 2017; WHO, 2019) classifies it into two broad categories based on its anatomical origin along the biliary tree. The first type is intrahepatic cholangiocarcinoma (iCCA), otherwise called peripheral CCA which accounts for 20% of CCA. It occurs within the liver, anatomically from the segmental bile duct (BD) and proximal to septal/interlobular BD and ductule (WHO, 2019). The other type is extrahepatic bile duct carcinoma (eBDC) which constitutes 80% of CCA. It comprises of tumors originating from large hepatic hilar bile duct (also known as Klatskin tumor) to distal extrahepatic BDs apart from those originating from Vater's ampulla (WHO,

2019). After hepatocellular carcinoma (HCC), iCCA is the second-most frequent cancer (Sakamoto et al., 2016). It accounts for 10-15% of primary liver cancers.

Intrahepatic Cholangiocarcinoma has further subtypes: (1) Large duct iCCA which arises in the large intrahepatic hilum and resembles perihilar and extrahepatic cholangiocarcinoma (Sakamoto et al., 2016; Nakanuma et al., 2003). The precursor lesions in background of which the large duct iCCA arises are Biliary Intraepithelial neoplasia and Intraductal Papillary neoplasm; Small duct iCCA which occurs in the hepatic periphery (WHO, 2019). The precursor lesions associated to small duct iCCA still remains unknown.

Here we are reporting an interesting case of large duct intrahepatic cholangiocarcinoma with bile duct showing intraductal papillary neoplasm with high grade dysplasia.

2. CASE REPORT

A 60-year-old male came with complaints of abdominal distension with history of dark coloured urine and clay coloured stool, history of pruritus, icterus and weight loss present. Laboratory investigations showed elevated serum ALP (Alkaline phosphatase) which was 215 IU/L (44-147 IU/L), elevated serum Bilirubin being 4.5 mg/dL (0.1-1.2 mg/dL) and serum CA 125 being 45 U/mL (0-5 U/mL). CECT (Contrast Enhanced Computed Tomography) abdomen revealed ill-defined peripheral enhancing hypodense lesion in segment IVA and II of liver causing mass effect on the hilum and intrahepatic biliary radicle dilatation. Few periportal, celiac and peripancreatic lymph nodes were noted along with hepatosplenomegaly. Therefore, a clinical diagnosis of intrahepatic cholangiocarcinoma with tumor extending into left portal vein, left hepatic duct including hilum and infiltrating into the hepatic artery with nodes metastasis was made. A left hepatectomy and cholecystectomy were performed and left lobe of liver and gall bladder along with lymph nodes were submitted for histopathology for the confirmation of the diagnosis.

Grossly we received left lobe of liver along with gall bladder (Figure 1). The resected left lobe of liver measured 14x12.5x7cm and weighed 375g. External surface had a glistening capsule (Figure 2) with a focal elevated area measuring 8x7cm. Cut surface revealed grey, white, firm tumor measuring 8x7.5cm in IVA and II segments of the liver (Figure 3). Tumor extended 0.1cm from the capsule and 0.1cm from the closest resected margin. Focal yellowish necrotic areas were also identified within the tumor. Adjacent liver parenchyma appeared greenish (bile stained) with focal areas of fibrosis. Grossly gall bladder measured 10x 2x 1cm and appeared congested. Cut surface revealed flattened mucosa, bile stained with thinned out wall. Also, six lymph nodes were present grossly where single largest lymph node measured 5.5x3x1cm and was firm in consistency.



Figure 1 Gross: Left lobe of liver with gall bladder



Figure 2 Gross: External surface of liver showing glistening capsule



Figure 3 Gross: Cut surface of liver showing grey, white firm tumor with focal yellowish necrotic area

Microscopic examination showed tumor of size 8x8x7.5cm with single tumor focality. The growth pattern of the tumor was mass forming and was confined to hepatic parenchyma. The arrangement of tumor cells was in ductal pattern with abundant fibrous stroma (Figure comprising of pleomorphic small to medium sized cuboidal to columnar cells having pale, slightly eosinophilic cytoplasm with small nuclei with desmoplastic reaction. Few foci showed mucous secretion (Figure 5). It was a

moderately differentiated tumor and was subtyped as Grade 2 type of large duct intrahepatic cholangiocarcinoma. Although liver somefoci showed liver with tumor infiltration, the hepatic parenchymal margin was uninvolved by the tumor. The bile duct margin and other margins were also uninvolved by the tumor. Both lymphovascular invasion (Figure 6) and perineural invasion (Figure 7) were present further affirming the diagnosis of large duct type. On examination of the lymph nodes all 6 lymph nodes were involved. Multiple areas of sampling of the tumor showed an intraductal papillaryneoplasm with high grade dysplasia (Figure 8 and 9).

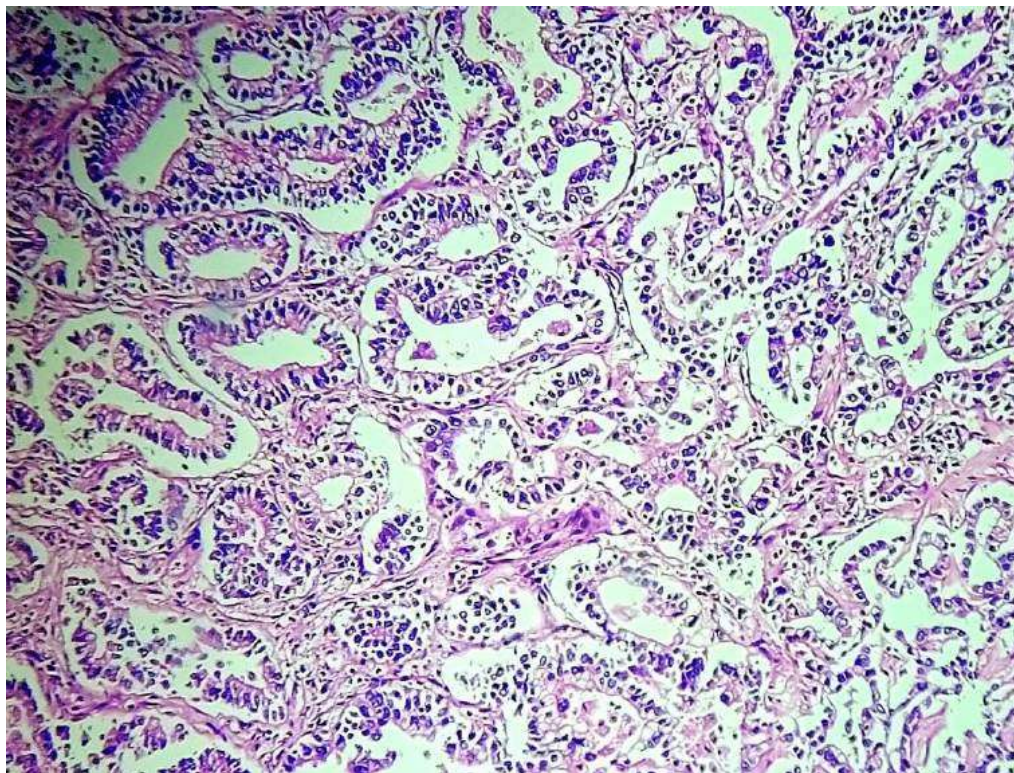


Figure 4 H & E: Low power (10X) view showing tumor cells arranged in acinar pattern separated by abundant fibrous stroma

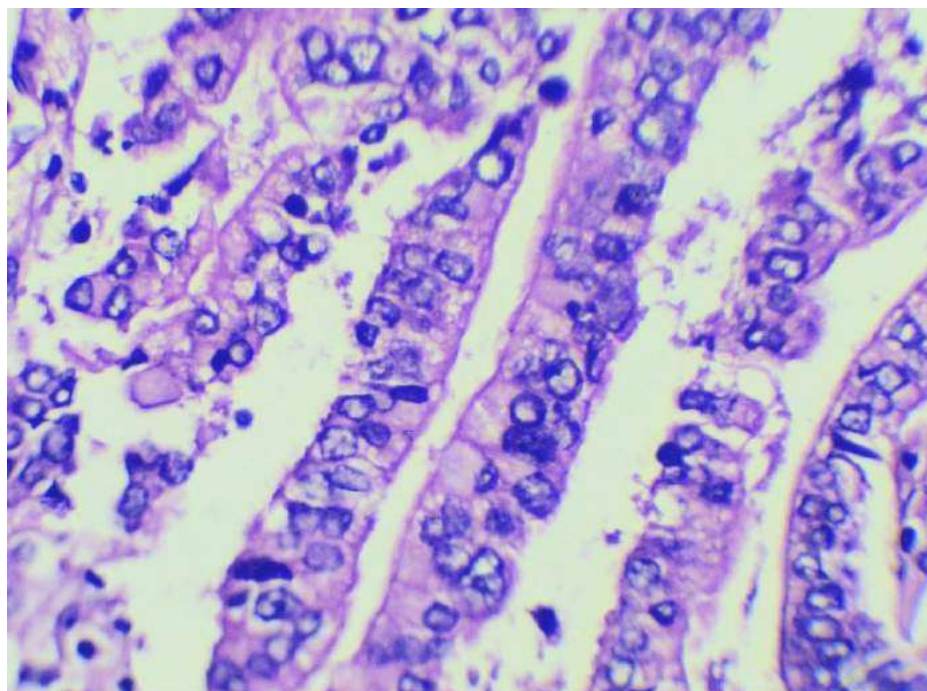


Figure 5 H & E High Power (40X) view showing mucous secretion

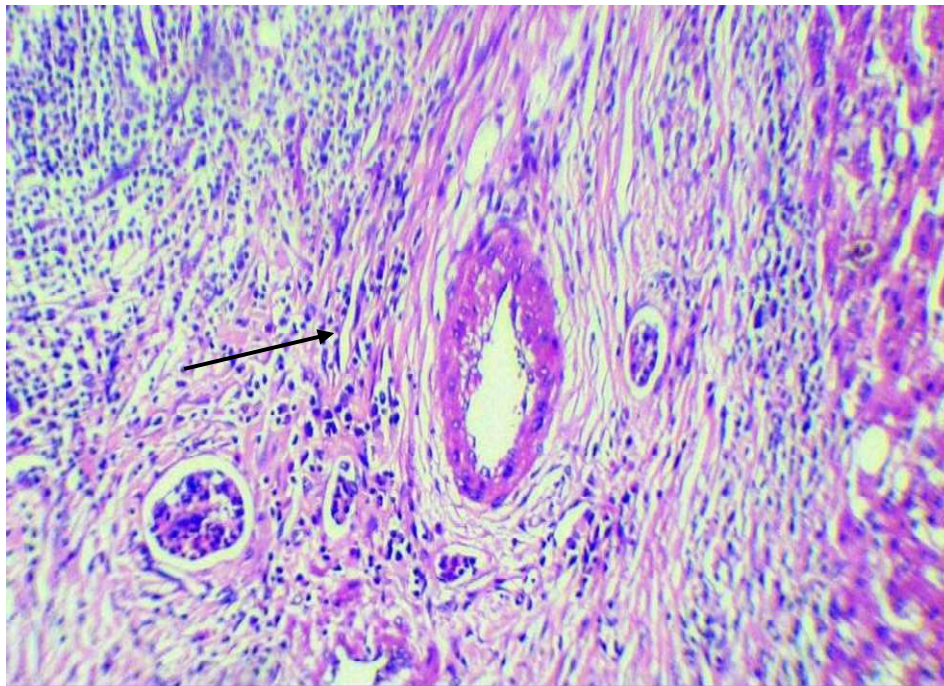


Figure 6 H & E High Power (10x) view showing lymphovascular invasion of tumor tissue

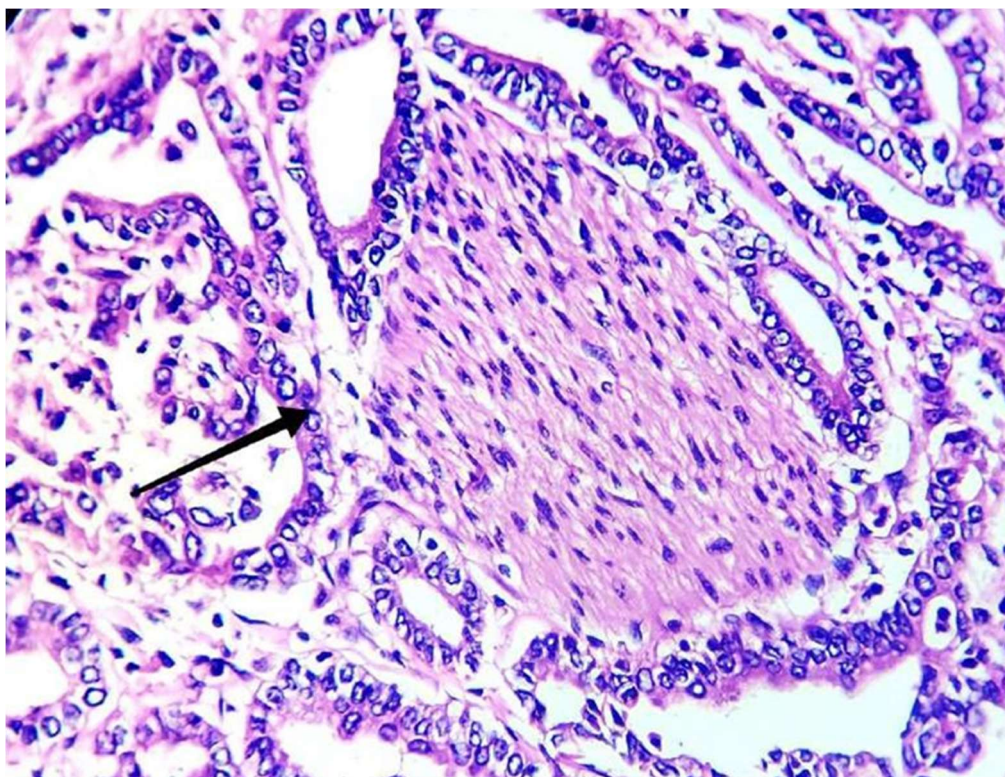


Figure 7 H & E High Power (40X) view showing perineural invasion of tumor tissue

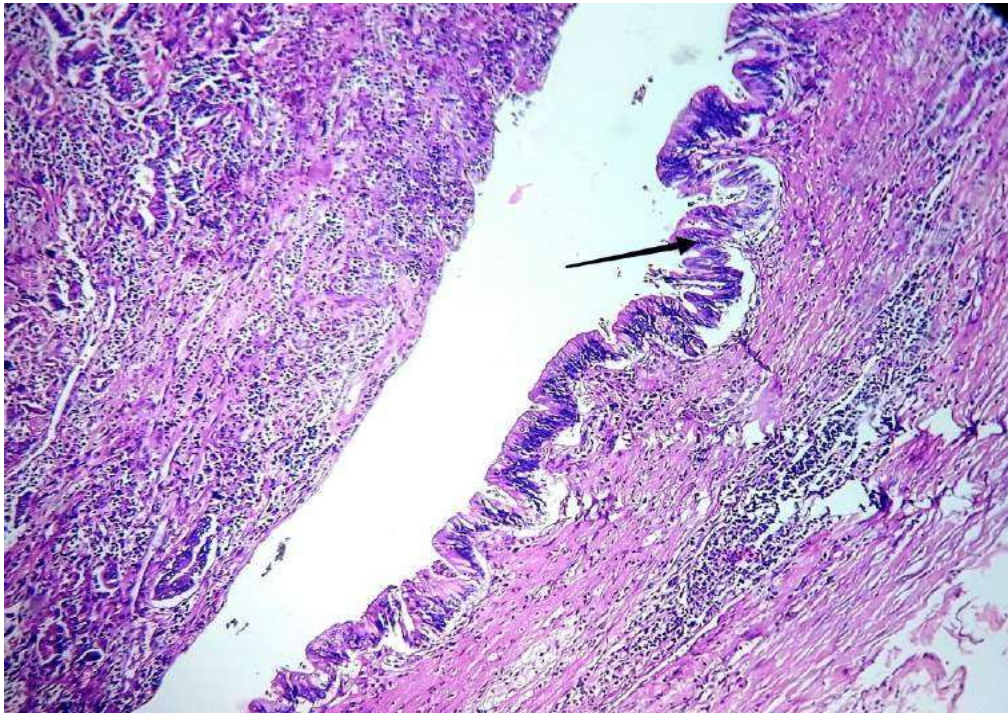


Figure 8 H & E: Low power (10X) view showing Intra ductal papillary neoplasm with high grade dysplasia

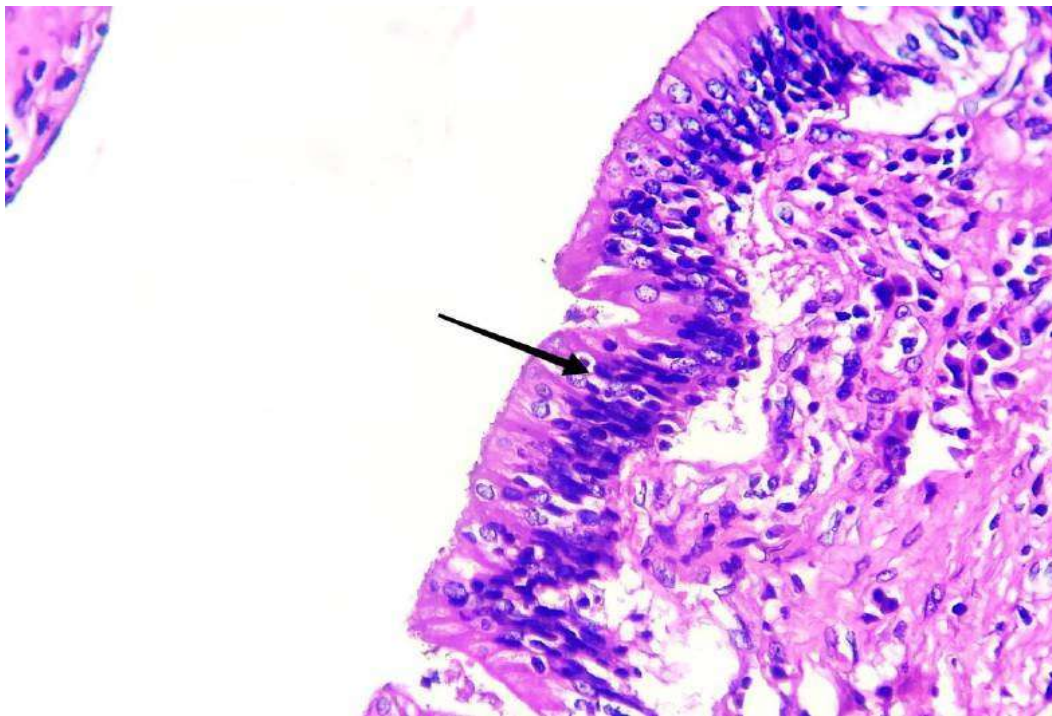


Figure 9 H & E: High power (40X) view showing intraductal papillary neoplasm with high grade dysplasia

Therefore, as per AJCC 8th edition tumor was classified as pT2pN1 Large Duct Intrahepatic Cholangiocarcinoma with bile duct showing 'intraductal papillary neoplasm with high grade dysplasia'.

3. DISCUSSION

After HCC, Intrahepatic cholangiocarcinoma (iCCA) accounts for the next most common type of primary liver cancer, constituting 10%-20% of all primary hepatic malignancies (Sakamoto et al., 2016; Nakanuma et al., 2003; Vijgen et al., 2017; Kitajima et al., 2007; Khan et al., 2005; Konstantinidis et al., 2016; Nakanuma et al., 2020). Various studies in recent past have revealed the increasing rates of iCCA globally (Kitajima et al., 2007; Malhi and Gores, 2006). Incidence of iCCA is more common in man than women. It is

usually diagnosed at a later stage and carries a poor prognosis (Nakeeb et al., 1996). The risk factors of iCCA include cirrhosis of the liver, primary sclerosing cholangitis, parasitic infections, hepatolithiasis, biliary duct cysts, chronic viral hepatitis, alcohol abuse, diabetes mellitus and obesity (Nakeeb et al., 1996; Chung et al., 2009). However, none of the risk factors mentioned above were present in our case. Adenocarcinoma differentiated at the biliary level, intrahepatic cholangiocarcinoma can arise from any intrahepatic biliary duct segment, including the small portal BDs, peripheral periportal ductules, to perihilar segmental ducts. At the same time iCCA can originate from hepatic progenitor cells (HPCs) (Brierley et al., 2016) or from the intrahepatic peribiliary glands (PBGs). The radiological features of iCCA include a broad range of findings demonstrating capsular retraction, satellite nodules and peripheral biliary dilatation (Brierley et al., 2016). The findings will depend on the size, location and components of the tumour (Doherty et al., 2017; Brandi et al., 2015). Thus, pathological diagnosis is the definitive diagnosis for appropriate treatment planning.

Macroscopically iCCA is classified into 3 types: Mass-forming, periductal infiltrating and mixed pattern (WHO, 2019; El-Diwany et al., 2019). (A) The first type-Mass-forming, which is made up of a lobulated solid mass with no microscopically appreciable link with the bile duct. It is known for its irregular but well-defined and unencapsulated borders; (B) The second type-periductal infiltrating, where the growth is along the bile duct and is not associated with any mass formation; (C) Third type-mixed pattern comprising of features of both mass-forming as well as periductal infiltrating type (WHO, 2019; Nakanuma et al., 2010). The present case of iCCA was of Mass forming type.

For better diagnostic approach recently, iCCAs have been classified into two subtypes as small and large duct (Sakamoto et al., 2016). Small duct type iCCA is a mass forming pattern and arises in the peripheral hepatic parenchyma. Although the risk factors for this includes non-biliary cirrhosis and chronic viral hepatitis, the precursor lesion for this type remains unknown (WHO, 2019). Histologically they are comprised of small ductal components presenting in a tubular pattern with low columnar type of cells to cuboidal cells. The ductular component shows cuboidal epithelia presents in a cord like pattern with slit like lumen and desmoplastic reaction (WHO, 2019; Ferrone et al., 2016). They usually consist of non-mucin secreting glands and morphologically closely resemble adenocarcinoma component of combined hepatocellular cholangiocarcinoma.

The large duct iCCA arises proximal to hepatic hilar region and can be both mass forming pattern and periductal infiltrating pattern. The risk factors for large duct iCCA are primary sclerosing cholangitis, hepatolithiasis and liver fluke infection (Nakeeb et al., 1996). The precursor lesion for large duct iCCA includes biliary intraepithelial neoplasia and intraductal papillary neoplasm. Histologically they show ductal or tubular pattern with columnar type of epithelium to the cuboidal epithelium type with desmoplastic reaction comprising of mucin secreting glands (WHO, 2019). Their histomorphological features are like that of perihilar cholangiocarcinoma. The characteristic features include MUC5AC, MUC6, S100, TTF1, AGR2, MMP7 and KRAS mutation (WHO, 2019).

Also, small duct type may or may not have perineural and lymphatic invasion whereas large duct type always presents with perineural and lymphatic invasion (WHO, 2019). In our case of large duct intraepithelial cholangiocarcinoma was associated with bile duct showing high grade dysplasia of intraductal papillary neoplasm which is known to be the precursor lesion of large duct iCCA. IPNB can occur at any level of the biliary tract and presents grossly as an exophytic growth in the lumen of dilated bile duct.

Histologically it presents as villous/papillary neoplastic epithelia along with fine fibrovascular stalks (Buettner et al., 2017) covered by tubular components. It is additionally divided into four subtypes- 1) Intestinal, 2) Gastric, 3) Pancreatobiliary and 4) Oncocytic. Based on epithelial features lining it, IPNBs can also be categorized as low-grade and high-grade. The newer classification by the Japan-Korea pathologist group classifies IPNB into two types: Type 1 which showed low grade and high-grade dysplasia with architecture being regular and Type 2 presented as exclusively high-grade dysplasia with architecture being irregular who was seen in our case (WHO, 2019; Buettner et al., 2017). This may be significant in the clinical field.

Latest genetic studies that have used the next-generation sequencing have revealed the presence of many genetic mutations such as: (i) IPNB which shows mutations in GNAS, KRAS and RNF43 are members to type 1, especially the intestinal subtype, which is similar to the mutations present in IPMN; (ii) IPNB lacking mutations. In KRAS, GNAS and RNF43 but having mutations in CTNNB1 are the member of pancreatobiliary subtype (Buettner et al., 2017; Ji et al., 2008). IPNB, which shows mutations of SMAD4, TP53 and PIK3CA may show complicated and other characterizing features of type 2 (Buettner et al., 2017). Therefore, recent designation of IPNBs can aid future clinical and fundamental studies including CCA with regards to the stage based on invasiveness of the neoplasm (pre and early invasive). Thus, a systemic approach that can lead to an early diagnosis with appropriate subtyping can undoubtedly result in a good prognosis and better outcome for the patients.

4. CONCLUSION

Intrahepatic cholangiocarcinomas are aggressive carcinomas with poor survival rates. Surgical resections have indicated a better prognosis. Macroscopic features like vascular invasion with advanced TNM staging and positive surgical margin usually results in a high recurrence rate. Amongst iCCA, small duct type has a better 5-year survival rate when compared to the large duct type, the probable reason being large duct iCCAs having higher pT stage when diagnosed and shows perineural infiltration very often. Notably, many variants of iCCA are described histologically which can exist together in the same tumor also.

In conclusion, considering the difficulty of obtaining a definitive preoperative diagnosis, performing surgery as a diagnostic treatment may be reasonable in cases involving tumors that exhibit characteristics of intrahepatic cholangiocarcinoma and other liver lesions without distant metastasis. Also, recognition of the precursor lesions like IPNB in our case which is a pre invasive neoplasm of bile duct carrying high risk of malignancy do facilitate a better understanding of pathogenesis and clinicopathological features of CCA at an early stage which would be helpful to decide the therapeutic modalities at pre invasive stage itself, resulting in better outcome of the disease. However, further studies would bring into limelight additional molecular and genomic studies which would further refine the classification resulting in better diagnostic and prognostic significance.

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Author Contributions

First author: Dr Neha A, Corresponding author: Dr J Thanka, others: Dr Rajendran, Dr Shobana B.

Informed consent

Written & Oral informed consent was obtained from the participant included in the study.

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Conflict of interest

The authors declare that there is no conflict of interests.

Data and materials availability

All data sets collected during this study are available upon reasonable request from the corresponding author.

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