

Case Report

MALIGNANT MASQUERADE – PROXIMAL TO THE HILUM

Niket Mayank Shah

Department of Surgical Gastroenterology, Sriramachandra Institute of Higher Education & Research, Chennai, Tamil Nadu, India.

Abstract

Cholangiocarcinoma is an aggressive malignancy and establishing a tissue diagnosis is the most complex problem especially in proximally located hilar biliary mass lesion. Mass at the hepatic hilum do not always represent malignancy. Few non-malignant processes affecting the extrahepatic biliary tree can mimic as malignancy. Benign pathological causes can be classified into five general categories (1) lymphoplasmacytic sclerosing pancreatitis and cholangitis (LPSPC), (2) Primary Sclerosing Cholangitis (PSC), (3) nonspecific fibroinflammatory process (NFIP), (4) granulomatous disease, and (5) stone disease. In the presence of a localized high bile duct mass or stricture without vascular involvement, it is impossible, without or even with biopsy or cytology, to make a definitive diagnosis. Multiple studies have shown that 5-15% of suspected malignant biliary mass/stricture have proved to be benign on pathology. Patients need to be counselled regarding the fact that biliary stricture may well be benign, but if benign disease were never resected then many cholangiocarcinoma would likely be underdiagnosed and undertreated.

Keywords: Biliary stricture; Malignant masquerade; Intrahepatic Cholangiocarcinoma

INTRODUCTION

Cholangiocarcinoma is an aggressive malignancy and a challenging disease to treat, with available literature emphasizing on surgical resection, newer imaging modalities, adjuvant therapy, and palliative therapy, but just establishing a tissue diagnosis itself is the most complex problem before treating such tumors especially in proximally located hilar biliary stricture. It is of paramount importance that the hepatobiliary surgeon should be familiar with the non-malignant processes that can affect the extrahepatic biliary tree mimicking as malignancy because major liver resections are still associated with a 30% to 50% morbidity and a 5% mortality.[1] Missing the diagnosis of a malignancy, however, is a fatal mistake.

Hadjis and associates [2] coined the phrase “malignant masquerade” to describe these non-malignant processes, further defined by Corvera and colleagues [3] as fibro-inflammatory processes at the hilum posing a difficulty in making a definitive diagnosis with certainty.

***Corresponding Author:** Niket Mayank Shah, Department of Surgical Gastroenterology, Sriramachandra Institute of Higher Education & Research, Chennai, Tamil Nadu, India.

Available literature demonstrate that the incidence of benign biliary lesions mimicking as malignant mass approaches around 15%. [4] Because of the generic inflammatory process of the masquerade, there have wide range of causes elucidated in the literature, some as simple as Mirizzi's syndrome, and others as obscure as a iatrogenic stricture of the bile duct by injection of a sclerosant as treatment for a bleeding duodenal ulcer. [5]

Here we present a case report of rare benign pathology masquerading as malignant biliary mass operated at our institute.

CASE REPORT

69 years age woman presented with chief complaints of dull aching upper abdominal pain for 3 months without any previous history of fever, jaundice, gastrointestinal bleeding or abdominal distension. Her vitals parameters were normal. On abdominal examination, mild tenderness was present at epigastric region with hepatomegaly 3 finger breath below costal margin with smooth surface. Hemogram and liver function parameters were normal. Patient underwent Ultrasound of abdomen which revealed few cystic lesions in left lobe of liver with dilated intrahepatic biliary radicals in left lobe with hepatomegaly and few small calculi within the gall bladder. Contrast enhanced CT abdomen [Fig 1, 2] was done which was suggestive of cholelithiasis and hepatomegaly (16.8 cm) with ill-defined heterogeneous intra-ductal and peri-ductal mass lesion of approximately 3*3*3cm involving left hepatic duct which was showing heterogenous enhancement on venous phase and progressive enhancement on delayed phase. The lesion was compressing left portal vein with chronic thrombosis of length around 3 cm. Left hepatic artery was encased within the lesion. There was proximal biliary dilatation in segment II, III and IVA. Multiple well defined thin walled non enhancing cysts without any internal septations or solid components seen in segment IVA largest measuring 4*3*5 cm. Segment II had another heterogenous lesion of size 2*1.5*2 cm. CA 19-9 was 95 IU/ML. Differential diagnosis were either left hepatic duct - mass forming cholangiocarcinoma or biliary cystadenocarcinoma with left portal vein chronic thrombosis and cholelithiasis. In view of radiologically evident resectable and highly suspicious malignant nature of lesion, left hepatectomy was planned. Patient and family members were counselled in detail about the nature the disease and need for surgical intervention in the form of resection of left lobe of liver. Diagnostic laparoscopy did not show any perito-

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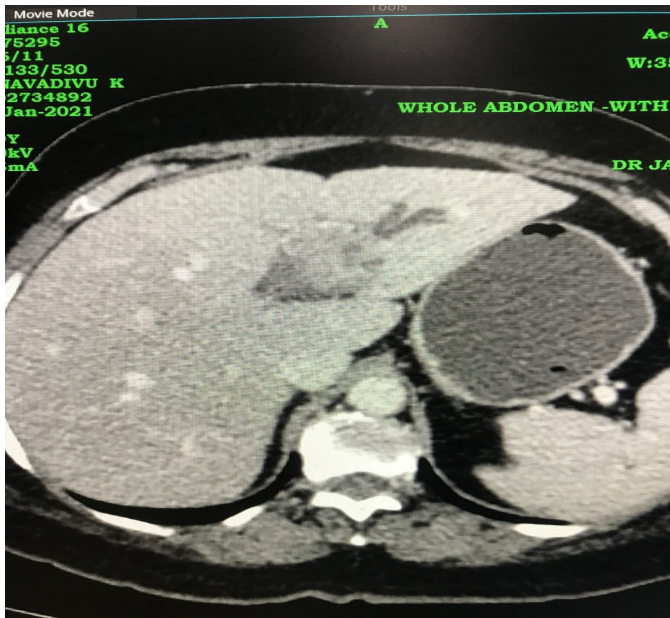


Figure 1: Axial Contrast enhanced CT abdomen showing heterogenous lesion at umbilical fissure region with proximal biliary dilatation

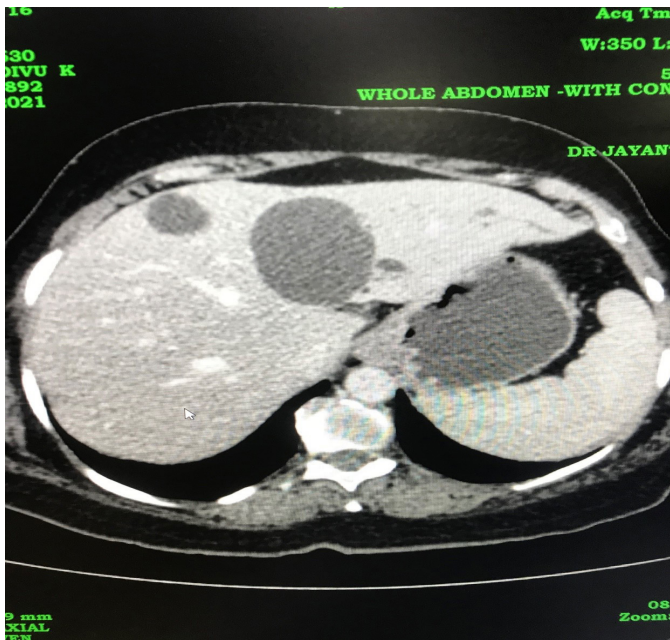


Figure 2: Axial CT scan showing multiple homogenous cystic lesions in segment IVA



Figure 3: Post operative specimen of left hepatectomy



Figure 4: Gross image of left lobe liver showing cystic lesions in segment II and segment IVA



Figure 5: Cut section showing multiple cystic lesions

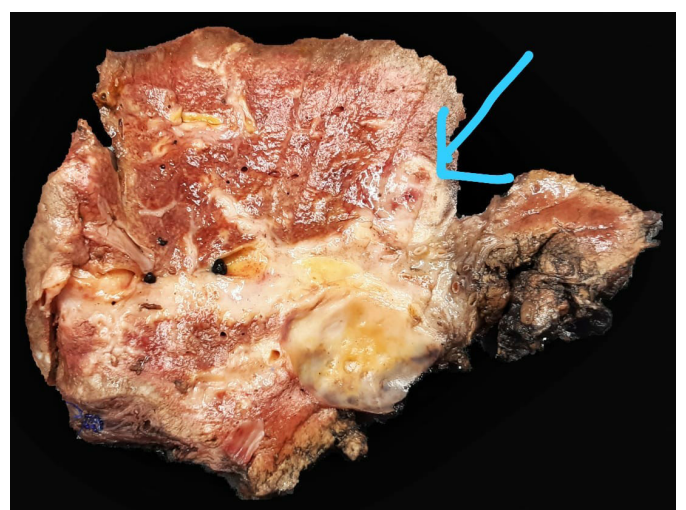


Figure 6: Cut section showing mass forming lesion with proximal biliary dilatation and intraductal calculi

neal, omental or pelvic metastatic deposits and hence patient underwent laparoscopy converted to open left hepatectomy in view of dense adhesions in the region of porta hepatis and specimen extracted [Fig 3]. Intra operative and post operative period were uneventful. Patient recovered well in post operative period. Macroscopic examination of left lobe liver specimen showed multiple thin walled cystic lesions with firm mass at the base of segment IVB [Fig 4]. Cut section showed fibrotic mass lesion at base of segment IVB with proximal biliary duct dilatation highly suspicious of malignant mass with few intraductal calculi in peripheral biliary radicals [Fig 5, 6]. On histological examination, however, no evidence of malignancy was found. H&E sections showed organised abscess formation showing dense inflammatory cells infiltrate consisting of neutrophils, lymphocytes and plasma cells and numerous histiocytes with chronic calculous cholecystitis [Fig 7, 8]. All cysts were proved to be benign simple cysts. As the plasma cells were very high in number with focal lamellar fibrosis, a diagnosis of IgG4 disease was suspected but immunohistochemical stain failed to show increase number of IgG4 cells. The presence of numerous macrophages were confirmed by the positive CD68 immunohistochemical stain [Fig 9]. A final diagnosis of Organising abscesses at left hepatic duct with secondary confluence involvement and multiple benign liver cysts with chronic cholecystitis was rendered.

DISCUSSION

Strictures at the hepatic hilum do not always represent malignancy.

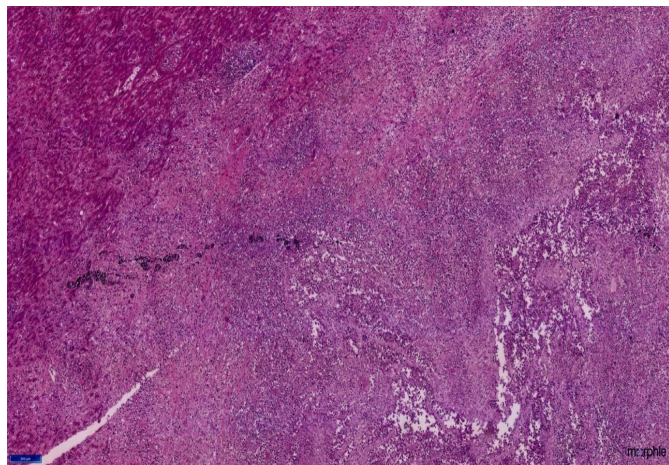


Figure 7: Histological section (10x) showing diffuse inflammatory cells infiltration

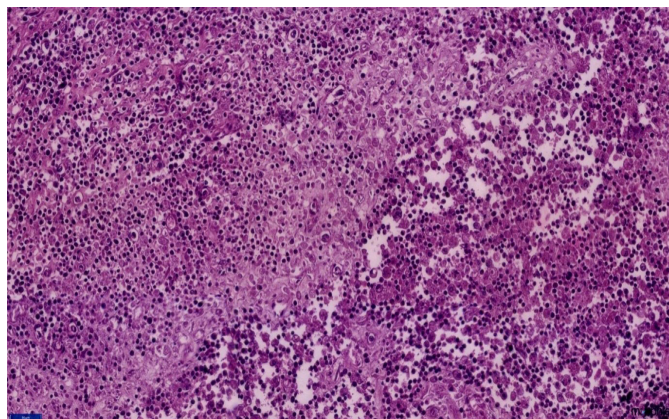


Figure 8: Histological section (40x) showing predominantly neutrophils, lymphocytes, plasma cells and histiocytes infiltration

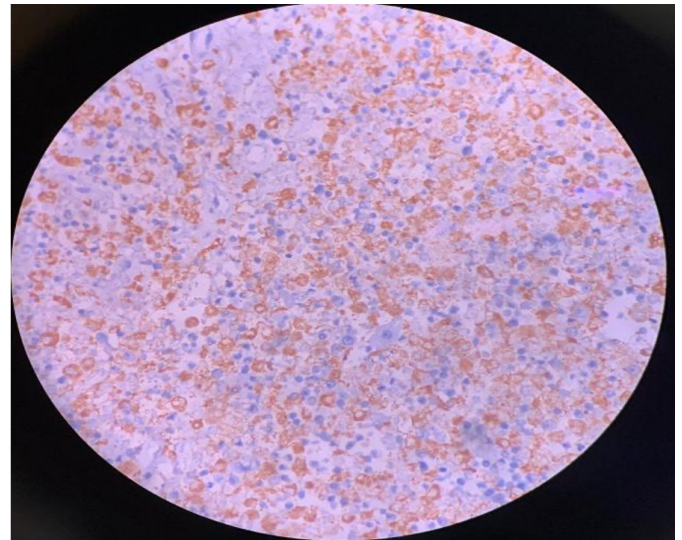


Figure 9: Histological section (40x) showing CD68 positive numerous macrophages

Wetter et al. [6] published their series of 98 patients with localized common hepatic duct stricture 8 of which were proved to be benign on pathology examination. In a series of 14 proximal bile duct strictures reported from Japan [7], all these patients had fibrosis of the bile duct with an inflammatory infiltrate. These benign strictures represents a spectrum of disease process with some may represent idiopathic fibrosis and others a form fruste of sclerosing cholangitis. There has been a report of eosinophilic cholangitis presenting as malignant masquerade [8] as well as tuberculosis stricture mimicking hilar cholangiocarcinoma [9]. Very often patients with suspicious biliary tract obstruction undergo a series of imaging studies including not only CT scan but MRI-MRCP, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC) and positron emission tomography (PET). These tests may show imaging pattern highly suggestive of malignancy, none of these are specific to accurately differentiate benign disease from malignant pathology. More than 85% of cholangiocarcinoma can have raised CA 19-9 but elevated CA 19-9 are found in multiple causes of benign stricture as well as malignant stricture [10]. Moreover, CA 19-9 cannot differentiate between pancreatic malignancy, gastric malignancy, or cholangiocarcinoma and has also been shown to be elevated in primary sclerosing cholangitis (PSC).

Carcinoembryonic antigen (CEA) has been found to be elevated in approximately 40-50% of patients of cholangiocarcinoma but they are found elevated in benign diseases like inflammatory bowel disease and severe liver injury. Many other markers like CA-125, CA-195, CA-242, DU-PAN-2, interleukin-6, and trypsinogen-2, have been tested but they all lack sensitivity as well as specificity to accurately predict benign versus malignant cause of underlying pathology.

Ultrasonography (USG) lacks sensitivity and specificity in differentiating benign versus malignant disease but helpful for ruling out stone disease as a possible cause of biliary although the presence of cholelithiasis does not necessarily exclude the possibility of concomitant cholangiocarcinoma. Garber and co-workers [11] found that the sensitivity of USG for defining a mass in the biliary tree is as low as 21% to 47% and positive predictive value is 94% and were also able to identify extensive regional lymphadenopathy, liver lesions, and portal vein in-

vasion, all of which are associated with malignant disease and much less likely with benign strictures. However it should be strongly noted that liver abscesses can appear like metastatic disease and adenopathy as well as portal vein thrombosis have been seen with benign inflammatory processes. In the series of 171 patients with hilar obstruction from Memorial Sloan-Kettering Cancer Centre, the presence of vascular invasion was strongly associated with a final diagnosis of cholangiocarcinoma as compared with benign disease [12]. The sensitivity of vascular invasion was highest when associated with lobar atrophy, which can also be seen on US, but which is very operator dependent. CT scan can provide tremendous information about extra and intra hepatic biliary tree, liver parenchyma, regional lymph nodes, vascular involvement and metastatic disease. Are and co-workers [12] demonstrated that vascular invasion occurs much more frequently in patients with malignancy, 58% versus 16% for patients with benign disease. Lobar atrophy was found in 41% of malignant stricture compared with only 6% of benign biliary stricture. Choi and co-workers [13] identified some findings observed significantly more in malignant stricture and may help in differentiating it from benign stricture: a stricture wall thicker than 1.5 mm; a longer involved segment of duct (17.9 mm +/- 6.6 mm for malignancy versus benign at 8.9 mm +/- 6.8 mm [$P < 0.0001$]); and a more dilated duct proximal to the obstruction (22 mm +/- 5.4 mm for malignancy versus benign at 17.8 mm +/- 4.6 mm [$P < 0.033$]). The hyperenhancement pattern of the involved bile duct wall during portal venous phase seen more commonly in malignant stricture compared with benign stricture. ($P < 0.0001$) Both ductal dilation and lymphadenopathy are not specific for malignancy. Lymphadenopathy can be present in inflammatory processes, such as PSC. Triple phase CT scan can identify vascular invasion and assess the resulting atrophy-hypertrophy.

If indicated, ERCP is chosen over PTC because most patients with obstructive jaundice have either choledocholithiasis or a periampullary neoplasm. PTC is often used when ERCP is unable to be performed, and is preferred in proximal biliary obstruction, especially the future liver remnant drainage is needed for surgery planning.

MRI-MRCP is highly sensitive for detecting biliary obstruction (72%–98%) but has less sensitivity in differentiating benign from malignant disease, with a wide range of sensitivities in the literature (30%–98%) [14]. Recently MRCP has been shown to be equivalent to both ERCP and PTC in the evaluation of benign versus malignant disease. Park and co-workers [14] and Rosch and co-workers [15] found out that all three modalities are equivalent at determining benign or malignant disease but lacking specificity. ERCP may provide a tissue diagnosis but often biopsy does not provide a tissue diagnosis either, especially for more proximal lesions. When a malignant diagnosis is being considered, contrast-enhanced MRI with MRCP can provide excellent information regarding the liver parenchyma (including atrophy-hypertrophy, and liver metastases), vascular invasion, and lymphadenopathy, and can be complementary to CT scan.

PET-CT scan can evaluate regional lymphadenopathy and distant metastasis more accurately and can upgrade some to unresectable or downgrade others to resectable disease compared with only conventional imaging, allowing curative resection for some and sparing others from an unwanted laparotomy [16]. PET currently lacks the sensitivity for diagnosing malignancy versus benign disease, especially

mucinous cholangiocarcinoma, which lacks FDG avidity.

Most biliary strictures, especially hilar stricture in patients without previous biliary tree manipulation and without stone disease, are mostly adenocarcinoma. Cytologically negative biopsy is more often false negative biopsy rather than a positive finding of benign biliary disease [12]. Previous studies demonstrate that the yield for brushings from ERCP or PTC have been positive in only 30% of patients with diagnosed cholangiocarcinoma [12,17]. The sensitivity was only 36% for ERCP with biopsy and 46% when brushings were performed in diagnosed cases of malignancy [18]. Some recent study showed higher sensitivity (70%-100%) and specificity (80%-95%) with biliary brush cytology for the early diagnosis of cholangiocarcinoma in PSC [19]. Corvera and co-workers showed that pathological causes can be classified into five general categories [3] (1) lymphoplasmacytic sclerosing pancreatitis and cholangitis (LPSPC), (2) PSC, (3) nonspecific fibroinflammatory process (NFIP), (4) granulomatous disease, and (5) stone disease. One more category should be considered as iatrogenic-idiopathic-autoimmune. Multiple case reports in the literature have shown benign biliary stricture development after an injection of sclerosant for duodenal ulceration, [5] as a consequence of non-Hodgkin's lymphoma, [20] pyogenic cholangitis, [21] atherosclerosis. [22] Several autoimmune processes such as systemic lupus erythematosus, Wegner's granulomatosis, and Sjogren's syndrome have been shown to cause biliary stricture [3,23]. In our patient, there were benign cysts with localised organised abscess formation at base of segment IVb masquerading as malignant mass necessitating an operative resection in the form of left hepatectomy to provide a cure.

CONCLUSION

In the presence of a localized high bile duct stricture and in the absence of vascular involvement, it is impossible, without or even with biopsy or cytology, to make a definitive diagnosis accurately. Cholangiocarcinoma is highly aggressive malignancy having poor prognosis with curative R0 resection as the only option for cure, but ability to obtain a definitive tissue diagnosis preoperatively for patients having radiographically resectable disease is unfortunately low. Multiple studies have shown that 5–15% of suspected malignant biliary stricture have proved to be benign on final pathology in spite of comprehensive preoperative workup with or without tissue biopsy. Unfortunately, no tests have ability to accurately differentiate between benign and malignant disease with high sensitivity and specificity. There are no confirmatory radiographic findings on USG, CT, MRI-MRCP, ERCP, EUS, or PET scan to define malignant versus benign disease. There is no laboratory value that can accurately diagnose biliary obstruction caused by adenocarcinoma. Patients need to be counselled regarding the fact that their biliary stricture may well be benign, but if benign disease were never resected then many cholangiocarcinoma would likely be underdiagnosed and undertreated.

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Conflict of interest: The author(s) declare that they have no competing interests.

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