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Case Report

Malignant Masquerade Proximal to the Hilum

Niket Shah[1]*, S Sankar[2] and S Rajendiran[3]

[1]Senior Resident, Department of Surgical Gastroenterology, Sriramachandra Institute of Higher Education and Research [SRIHER], Chennai, India

[2]Professor, Head, Department of Surgical Gastroenterology, Sriramachandra Institute of Higher Education and Research [SRIHER], Chennai, India

[3]Professor, Department of Pathology, Sriramachandra Institute of Higher Education and Research [SRIHER], Chennai, India

***Corresponding Author:** Niket Shah, Senior Resident, Department of Surgical Gastroenterology, Sriramachandra Institute of Higher Education and Research [SRIHER], Chennai, India.

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Abstract

Introduction: Cholangiocarcinoma is an aggressive malignancy and establishing a tissue diagnosis is the most complex problem especially in proximally located hilar biliary stricture. Few non-malignant processes affecting the extrahepatic biliary tree can mimic malignancy. Hadjis and associates [2] coined the phrase ''malignant masquerade'' to describe 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. Here we present a case report of a rare benign pathology masquerading as malignant biliary stricture.

Case Report: A 69-year-old woman presented with abdominal pain of 3 months duration was diagnosed to have highly suspicious malignant biliary stricture at base of liver segment IVB with proximal biliary dilatation with multiple benign looking hepatic cysts in segments II and III and cholelithiasis. CA 19-9 was 95 U/ML. In view of suspicious left hepatic duct cholangiocarcinoma, the patient underwent left hepatectomy. Biopsy was reported as chronic organized abscess formation with dense inflammatory infiltrates and chronic cholecystitis.

Strictures at the hepatic hilum do not always represent malignancy. Corvera and co-workers showed that benign pathological causes can be classified into five general categories: lymphoplasmacytic sclerosing pancreatitis and cholangitis (LPSPC), PSC, nonspecific fibroinflammatory process (NFIP), granulomatous disease, and stone disease.

Conclusion: In the presence of a localized high bile duct 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 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 cholangiocarcinomas 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 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 im-

portance that the hepatobiliary surgeon be familiar with the non-malignant processes that can affect the extrahepatic biliary tree, which can mimic malignancy because major liver resections are still associated with 30% to 50% morbidity and 5% mortality [1]. However, Missing the diagnosis of a malignancy, 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.

Available literature demonstrates that the incidence of benign biliary stricture mimicking malignant stricture approaches 15% [4]. Because of the generic inflammatory process of the masquerade, there are a wide range of causes elucidated in the literature, some as simple as Mirizzi's syndrome, and others as obscure as an 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 a rare benign pathology masquerading as a malignant biliary stricture operated at our institute.

Case Report

A 69-year-old woman who presented with chief complaints of dull, aching upper abdominal pain that has persisted for three months, with no history of fever, jaundice, gastrointestinal bleeding, or abdominal distension. On abdominal examination, mild tenderness was present at the epigastric region with hepatomegaly, three finger below right costal margin with smooth surface. The hemogram was normal. Liver function parameters were normal. Contrast enhanced CT abdomen [Figure 1] was suggestive of cholelithiasis and hepatomegaly (16.8 cm) with an ill-defined heterogeneous intra-ductal and peri-ductal mass lesion of approximately 3×3×3 cm in the hilar region involving primary confluence with the left hepatic duct which was showing heterogenous enhancement in the venous phase and progressive enhancement in the delayed phase. The lesion was compressing the left portal vein with chronic thrombosis length of about 3 cm. The left hepatic artery was encased within the lesion. There was proximal biliary dilatation in segments II, III and IVA. Multiple well-defined thin-walled non enhancing cysts without any internal septations or solid components are seen in segment IVA, the 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 hilar region-left hepatic duct confluence region mass forming cholangiocarcinoma or biliary cystadenocarcinoma with left portal vein chronic thrombosis. In view of the radiologically evident resectable and highly suspicious malignant nature of the lesion, left hepatectomy was planned. Liver volumetry analysis was suggestive of an adequate right lobe future liver remnant. Diagnostic laparoscopy was normal, and the patient underwent left hepatectomy. Intraoperative and postoperative periods were uneventful. Gross examination of the left lobe liver showed multiple thin-walled cystic lesions with a firm mass at the base of segment IVB. Cut section showed fibrotic mass lesion at segment IVB with proximal biliary duct dilatation highly suspicious of malignant mass [Figure 2, 3]. On histological examination, however, no evidence of malignancy was found. Haematoxylin and eosin sections showed organised abscess formation with a dense inflammatory cell infiltrate consisting of neutrophils, lymphocytes, and plasma cells and numerous histiocytes with chronic calculous cholecystitis. A diagnosis of IgG4 disease was suspected as the plasma cells are very high in number with focal lamellar fibrosis. Immunohistochemical staining failed to show an increased number of IgG4 cells [Figure 4]. And the presence of numerous macrophages is confirmed by the positive CD68 immunohistochemical stain. A final diagnosis of organising abscesses of the liver was rendered.

Figure 1: Axial Contrast enhanced CT abdomen showing heterogenous lesion in segment IV with proximal biliary dilatation

Figure 2: Cut section showing multiple cystic lesions, largest measuring 2.1 cm.

Figure 3: Cut section showing mass forming lesion with proximal biliary dilatation.

Figure 4: Infiltration made up of predominantly neutrophils, lymphocytes, plasma cells and histiocytes (H&E, x40).

Discussion

Strictures at the hepatic hilum do not always represent malignancy. Wetter., *et al*. [6] published their series of 98 patients with localized common hepatic duct strictures, 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 of these patients had fibrosis of the bile duct with an inflammatory infiltrate. These benign strictures represent a spectrum of disease processes with some representing idiopathic fibrosis and others a form of fruste of sclerosing cholangitis. There has been a report of eosinophilic cholangitis presenting as a malignant masquerade [8] as well as tuberculosis stricture mimicking hilar cholangiocarcinoma [9].

Patients with suspected biliary tract obstruction are frequently subjected to a battery of imaging tests, including CT scans, MRI-MRCP, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), and positron emission tomography (PET).These tests may show imaging patterns highly suggestive of malignancy, but none of these are specific enough to accurately differentiate benign disease from malignant pathology.

More than 85% of cholangiocarcinoma's can have elevated CA 19-9. Elevated CA 19-9 are also 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 with cholangiocarcinoma, but it is also 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, lack sensitivity as well as specificity to accurately predict benign versus malignant causes of underlying pathology.

Ultrasonography (USG) lacks sensitivity and specificity in differentiating benign versus malignant disease but is helpful in ruling out stone disease as a possible cause of biliary obstruction, 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 the positive predictive value is 94%. They were also able to identify extensive regional lymphadenopathy, liver lesions, and portal vein invasion,

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 Center, the presence of vascular invasion was strongly associated with a final diagnosis of cholangiocarcinoma as compared with benign disease [12].

CT scan can provide tremendous information about extra and intra hepatic biliary tree, liver parenchyma, regional lymph nodes, vascular involvement, and metastatic disease. 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 the portal venous phase is 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. 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 strictures compared with only 6% of benign biliary strictures.

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

MRI-MRCP is highly sensitive for detecting biliary obstruction (72%-98%) but less sensitive for distinguishing benign from malignant disease, with a wide range of sensitivities reported 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 in determining benign or malignant disease but lack specificity. ERCP may provide a tissue diagnosis but often a biopsy does not provide a tissue diagnosis either, especially for more proximal lesions.

PET currently lacks the sensitivity for diagnosing malignancy versus benign disease, especially mucinous cholangiocarcinoma, which lacks FDG avidity [16].

Most biliary strictures, especially hilar strictures in patients without previous biliary tree manipulation and without stone disease, are mostly adenocarcinoma. Cytologically negative biopsy is more often a 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 has 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 studies 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] lymphoplasmacytic sclerosing pancreatitis and cholangitis (LPSPC), PSC, nonspecific fibroinflammatory process (NFIP), granulomatous disease, and 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], and 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 chronic abscess formation at the base of segment IVb masquerading as malignant stricture necessitating an operative resection in the form of left hepatectomy to provide a cure. To our knowledge, a pathological process has not been described in the literature.

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 a highly aggressive malignancy with a 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 strictures have proved to be benign on final pathology in spite of comprehensive preoperative workup with or without tissue biopsy. Unfortunately, no tests can accurately differentiate between benign and malignant diseases 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 test 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 cholangiocarcinomas would likely be underdiagnosed and undertreated.

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