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Case Report

Biliary metastasis in colorectal cancer confers a poor prognosis: case study of 5 consecutive patients

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The biliary duct is an extremely rare site for colon cancer metastasis. It often leads to a diagnostic dilemma, since primary cholangiocarcinoma (potentially treatable with surgery) has a similar presentation. This paper highlights our experience with 5 consecutive patients who had colon malignancy with biliary metastasis, and prognosis of their disease. Five patients, with a history of primary colon cancer since 2010, were identified to have biliary metastasis. Of these, 4 (80.0%) patients were male. The median time to diagnosis of biliary metastasis from diagnosis of colon cancer was 59.2 months (0-70.1 months), and all exhibited symptoms of biliary obstruction or its associated complications. Evaluation of the tumour samples revealed all specimens to be negative for CK7 but positive for CK20, suggestive of a colorectal primary. The median survival of the 5 patients was 23.5 months (1.8-44.5 months) from the diagnosis of biliary metastasis. However, none of their death was related to the direct complication of biliary obstruction. Biliary metastasis is a rare entity for metastatic colon malignancy. Diagnosis may be difficult radiologically, and immunohistochemical staining may help in identification. The overall survival for these patients is dismal. **(Ann Hepatobiliary Pancreat Surg 2017;21:57-60)**

Key Words: Bile Duct; Colorectal Cancer; Prognosis; Metastasis

INTRODUCTION

Metastasis to the bile duct is an extremely rare manifestation of colon cancer.[1,2] Due to its rarity, the symptoms, best modality of investigations, and prognosis are not clear. This study therefore aims to review our institution's experience in managing 5 patients with biliary metastasis.

This was a retrospective review from a single institution. All patients were above the age of 21, and were diagnosed with biliary metastasis, secondary to a colonic primary detected in 2010. Biliary metastases were confirmed using histopathological methods; immunohistochemistry confirmed the colonic primary. Patients were identified using a pre-existing colorectal cancer database. Details of the cases, including patient demographics, histopathological characteristics, investigation details, and oncological progress, were collected.

CASE

Patient demographics

Biliary metastatic adenocarcinoma was histologically diagnosed in 5 patients, who had a prior history of primary colon cancer since 2010. The median age of diagnosis of colon cancer for these patients was 57 years (49-78 years). Family history of colorectal malignancy was negative for all 5 patients. Demographics of all patients are provided in Table 1.

The median time from diagnosis of colon cancer to biliary metastasis was 59.2 months (0-70.1 months). All patients presented with symptoms and biochemical outcomes for obstructive jaundice or persistent unresolved transaminitis. Prior to the development of biliary metastasis, the primary colonic tumour had been resected in 3 patients (60.0%). These 3 patients developed an ex-

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tra-colonic metastatic disease before the development of biliary metastasis. In 1 patient (20.0%), metastasis had already progressed to the biliary system, lung and liver, at the time of diagnosis of colon cancer. Intra-hepatic and extra-hepatic biliary duct involvement was seen in 2 patients (40.0%). Table 2 provides details of the oncological characteristics of the patients.

In all cases, the primary colon tumour was either located in the sigmoid colon (n=3, 60.0%) or the ascending colon (n=2, 40.0%). All primary tumours were moderately differentiated in terms of tumour grade, with only 2 (40.0%) exhibiting microscopic features of aggressive tumour biology (mucinous, lymphovascular invasion, perineural invasion). None of the tumours were positive for KRAS mutation.

Radiological appearance

Fig. 1 depicts how the intra- and extra-hepatic biliary ductal dilation secondary to a biliary stricture mimics the radiological appearance of a primary cholangiocarcinoma. Also, with imaging using magnetic resonance cholangiopancreaticogram (MRCP), the endoluminal biliary metastasis at the confluence of the right and left hepatic ducts can be easily mistaken as cholangiocarcinoma (Fig. 1), thus highlighting the difficulty in differentiating both pathologies using only radiological investigations.

Malignant characteristics

Tumours resected from all 5 patients Immunohistochemical staining for biliary brushings from tumours of all 5 patients were positive for CK20, but negative for CK7. Three samples assessed for CDX2 were positive.

Surgical and oncological outcomes

Biliary stents were inserted in 4 patients (80.0%) during endoscopic retrograde cholangio-pancreaticography (ERCP), while 1 patient had a percutaneous transhepatic cholangiogram (PTC) with drain insertion, due to extra-hepatic biliary obstruction from the metastasis.

Three patients demised at the hospital, while one was discharged to the hospice; the last patient has been lost to follow up since 2012. The median time to death/last seen alive from the diagnosis of biliary metastasis was 23.5 months (1.8-37.2 months).

Table 1. Patient demographics

Variable	n (%)
N	5
Male	4 (80.0)
Ethnicity	
Chinese	3 (60.0)
Malay	2 (40.0)
Median age at: (range, in years)	
Diagnosis of colon cancer	57 (49-78)
Diagnosis of biliary metastasis	62 (55-78)

Table 2. Malignancy characteristics

Variable	n (%)
Location of primary colon tumor	
Ascending colon	2 (40.0)
Sigmoid colon	3 (60.0)
Tumor histology	
Adenocarcinoma	5 (100.0)
Aggressive tumor characteristics	
Mucinous tumor	1 (20.0)
Lymphovascular invasion	1 (20.0)
Perineural invasion	1 (20.0)
KRAS mutation	0
Chemotherapy	
Neo-adjuvant	0
Adjuvant	3 (60.0)
Palliative	1 (20.0)
Median time from diagnosis of colon cancer to diagnosis of biliary metastasis/months (range)	51.2 (0-65.2)
Location of other sites of metastasis	
Lung	4 (80.0)
Liver	3 (60.0)
Adrenals	1 (20.0)
Bladder	1 (20.0)
Peritoneum	1 (20.0)
Presenting complaint	
Jaundice	4 (80.0)
Abdominal pain	3 (60.0)
Transaminitis	1 (20.0)
Liver function at time of diagnosis of biliary metastasis	
Raised bilirubin	4 (80.0)
Raised aspartate aminotransferase	3 (60.0)
Raised alanine aminotransferase	2 (40.0)
Raised alkaline phosphatase	5 (100.0)
Decreased albumin	1 (20.0)
Computed tomography findings	
Intrahepatic involvement	1 (20.0)
Extrahepatic involvement	1 (20.0)
Both	3 (60.0)
Immunohistochemical tests	
Cytokeratin 7 negative	5 (100.0)
Cytokeratin 20 positive	5 (100.0)
CDX2 positive	3 (60.0)
Median time from diagnosis of biliary metastasis to death/last seen alive/years (range)	2.0 (0.6-3.1)

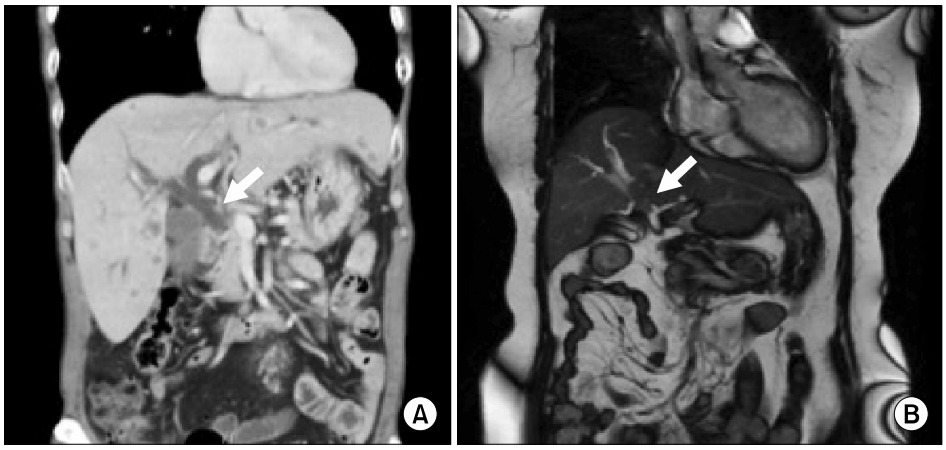

Fig. 1. Radiological imaging of biliary metastasis. The computed tomography scan (A) of a patient with distal common bile duct metastatic stricture, and a magnetic resonance cholangiopancreaticogram (B) of another patient with biliary metastasis at the confluence of the right and left hepatic ducts.

DISCUSSION

Biliary metastasis from colon cancer is an extremely rare manifestation of colon cancer since its first report by Herbut and Watson[3] in 1946. Some suggest that isolated intrahepatic biliary metastasis can be regarded as a variant of hepatic metastasis which are less aggressive and have a better prognosis than the typical parenchymal liver metastasis of colon cancer.[4-9] Two different morphologies of biliary metastasis have been described: one being malignant biliary stricture, and the other as an endoluminal lesion.[2,10]

In our study, most of our patients presented with jaundice, and all of them underwent a Computed Tomography scan. Because of the intrahepatic ductal dilatation seen in majority of their scans, the initial diagnosis was cholangiocarcinoma. The diagnosis of biliary metastasis was achieved only after the immunohistochemical staining revealed that all the biliary tumour were positive for CD20 and negative for CD7, suggesting that the tumor possibly originated from intestinal origin, thus highlighting the importance of immunohistochemistry in the diagnosis of biliary metastasis of colon cancer; this is also highlighted in several other reports.[11-13]

Advances of immunohistochemistry in the field of oncology has allowed the increased use of low-molecular weight cytokeratins to help differentiate the origins of metastatic disease, and guide in the management of synchronous or metachronous tumors.[11] Anatomical origins not known to express CK 7 include the colon, prostate, kidney, thymus, carcinoid tumors of lung and gastrointestinal tract, as well as Merkel cell tumour of the skin. Primary cholangiocarcinoma tend to express CK 7.[14] On the other hand, all colorectal carcinoma and Merkel cell tumors express CK 20, while some proportion of pancreatic, gastric, translational cell and less than half of the cholangiocarcinomas also express this cytokeratin. As such, by combining various cytokeratin expressions will enable us to more accurately differentiate the origin of the tumor cells in cases of possible metastasis.

Despite the use of immunohistochemistry, the accurate diagnosis remains difficult and it is important to consider differentials. Primary cholangiocarcinoma needs to be differentiated from locally invasive tumors like hepatocellular carcinoma if the dilatation is more proximal, and from periampullary tumors (duodenal, ampulla of Vater or head of pancreas) for the more peripheral bile ducts. Common sites of primary for biliary metastases include the colon and gastric carcinoma.

Our study also showed that prognosis after the development of biliary metastasis from colorectal cancer is poor. The 5-year survival from the time of biliary metastasis is dismal at 0%, with the median time of death being approximately 2 years (0.6-3.1 years). Our result is similar to those reported at the Sloan-Kettering Cancer Centre, where the 5-year survival rates for unresected biliary metastasis is 0%.[15] Patients who develop biliary metastasis also suffer significant morbidity with repeated episodes of hepatobiliary sepsis due to biliary obstruction, requiring admission, antibiotics and invasive procedures like PTC and drainage, or ERCP with stent insertion, which carries further procedural risks like pancreatitis, stent related complications like blockage, and even duodenal perforation.

Therefore, it is essential that clinicians bear in mind

that a presentation of obstructive jaundice in patients with a prior history of colon malignancy has the possibility of developing biliary metastasis, even though it is extremely rare. This will enable the clinician to utilize immunohistochemical stains as part of the diagnostic work-up. This is particularly important as the management and prognosis of cholangiocarcinoma and biliary metastasis is markedly different, and would affect the approach for subsequent counselling.

In conclusion, though rare, biliary metastasis must remain a differential when reviewing a patient presenting with painless jaundice, having prior history of colon malignancy. Immunohistochemical tests may be necessary to differentiate it from primary cholangiocarcinoma. However, development of biliary metastasis confers a poor outcome in terms of survival.

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