Simultaneous gallbladder and bile duct cancers: revisiting the pathological possibilities


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Abstract

The pathogenesis of gallbladder cancer presenting synchronously with malignancy of the bile duct has not been clearly understood. The possible causes for the simultaneous presence of these tumors could be due to local spread, metastases, de novo multifocal origin, or as part of a field change in the extrahepatic biliary apparatus. In this article, we discuss the cases of four patients with simultaneous gallbladder and bile duct malignancies and analyze their individual pathologies to provide an explanation into the mechanisms that may play a role in such conditions.

Key Words: Cancer, cholangiocarcinoma, field cancerization, gall bladder, synchronous

Introduction

Synchronous malignancies within the extrahepatic biliary tree are a rare cause for and there may be the simultaneous presence of gallbladder cancer coexisting with bile duct cholangiocarcinoma. The possible explanations for such an occurrence could range from the rare synchronous malignancies to local spread, to metastasis.

The majority of cases of synchronous malignancies reported are from Japan [1-4], where malignancies are usually associated with anomalous pancreatic bile duct junction (APBDJ). This association with APBDJ is not an absolute necessity, as shown by Kurosaki et al. [5] in a series of seven patients. An often confused clinical scenario has been that of local metastasis from a primary in the biliary tree leading to the misdiagnosis of synchronous malignancy. Warren et al. [6] and Gertsch et al. [7] have attempted to describe criteria for differentiation of the two conditions.

Over the past few decades, the reasons for labeling extrahepatic biliary cancers as synchronous have been based on multifocal origin [8]. The criteria for differentiating between synchronous primaries and metastasis are still being developed [9]. Gallbladder cancer, in patients without APBDJ, does not follow the adenoma-carcinoma but rather the dysplasia in situ invasive carcinoma sequence [10,11].

The field cancerization theory was first introduced in 1953 by Slaughter when describing the concept in the aerodigestive tract [12]. This concept has been used to explain the possibility of distant related primary tumors in the upper aerodigestive tract [13].

The p53 gene mutations have been closely associated with determination of clonality [13]. Allelic loss or deletions at the TP53 locus (17p13) have been reported ranging from 58% to 92% in gallbladder cancer [14,15]. These deletions have been noted at histologically normally appearing epithelium near gallbladder cancer [14].

In discussing the cases of four random patients with simultaneous gallbladder and bile duct malignancies who presented to us, our aim was to describe the various pathological possibilities in which gallbladder cancer may occur synchronously with a malignancy of the extra-hepatic bile duct.
Case reports

Case 1
A 49-year-old male referred to us with obstructive jaundice and pruritis that had developed over 2 months. He had undergone endoscopic retrograde cholangiopancreatography (ERCP) with papillotomy and stenting with a 10Fr plastic stent in view of a stricture of the lower common bile duct (CBD). On examination, the patient was icteric and generally well preserved. His blood examination revealed direct hyperbilirubinemia (serum bilirubin = 2.80 mg/dl) with a CA19-9 level of 0 units/ml. A targeted endoscopic ultrasound (EUS) was performed which showed a hypoechoic tumor in the lower CBD extending to the pancreas (uT4N0) (Figure 1a). A contrast-enhanced computed tomography (CT) scan of the abdomen (Figure 1b) showed a mild thickening of the fundus of the gall bladder with altered attenuation extending into segment IVB of the liver. There was intrahepatic biliary dilatation with evidence of CBD stent in situ. The patient was taken for surgery, where the findings were a neoplastic mass in the fundus of the gall bladder infiltrating the liver with pericholedochal lymphadenopathy. There was another separate neoplastic mass in the lower CBD. An extended cholecystectomy with extrahepatic CBD excision with a pancreaticoduodenectomy with radical lymphadenectomy was performed (Figure 1c, d). Intra-operative ultrasonography was done to rule out other lesions in the pancreas as well as metastasis in the liver. A frozen section confirmed the negative proximal margin of the CBD. Postoperative histopathology revealed a poorly differentiated adenocarcinoma of the gallbladder (T3N1) along with a poorly differentiated adenocarcinoma of the lower CBD (T3N1) with no anatomical continuity between the two tumors with a solitary lymph node metastasis. The patient is disease-free at 5 months’ follow-up.

Case 2
A 49-year-old male presented to us with obstructive jaundice and pruritis that had developed over 1 month. On examination, the patient was icteric with a palpable gall bladder. His blood examination revealed direct hyperbilirubinemia (serum bilirubin = 27.19 mg/dl) with a CA19-9 level of 117322 units/ml. ERCP revealed a stricture extending from the proximal to the mid-CBD. In view of the suboptimal general condition of the patient with respect to surgical risk, the decision was taken to perform an ERCP with stenting with the relief of jaundice prior to surgery. Papillotomy was performed and a 10Fr plastic stent was placed. The patient developed post-ERCP pancreatitis, which was mild and settled with conservative management. Once the episode of acute pancreatitis subsided, a contrast-enhanced CT scan of the abdomen (post-ERCP) was performed which showed a distended gallbladder with dilatation of the intrahepatic biliary radicles in both lobes of the liver. The patient underwent surgical exploration, which revealed a neoplastic mass in the neck of the gall bladder contiguous with the hilar cholangiocarcinoma. An extended extrahepatic bile duct excision with cholecystectomy was performed. However, the entire biliary tree down to the intrapancreatic portion
of the CBD, distally, and the right and left hepatic ducts (proximally), revealed dysplasia on frozen section (field cancerization). A hepaticojejunostomy was performed and the patient was pencilled in for postoperative intrabiliary radiotherapy. Postoperative histopathology revealed a moderately differentiated adenocarcinoma of the neck of the gallbladder, cystic duct, common hepatic duct (CHD), and CBD. Lymphovascular emboli and perineural invasion were seen. Both the proximal and distal cut margins showed evidence of tumor. The patient is disease-free at a follow-up of 6 months.

Case 3

A 56-year-old male presented to us with obstructive jaundice and pruritis that had developed over 1 month. On examination, he was jaundiced with a palpable lump in the right hypochondrium. His blood examination revealed direct hyperbilirubinemia (serum bilirubin = 16.30 mg/dl) with a CA19-9 level of 38.75 units/ml. A contrast-enhanced CT of the abdomen showed a short segment tight stricture in the proximal CBD, just beyond the confluence, suggestive of a cholangiocarcinoma. Preoperative Doppler ultrasound showed involvement of the anterior branch of the right hepatic artery with no involvement of the portal vein. In view of the good general condition of the patient with a normal coagulation profile, it was decided to subject him to surgery without preoperative stent placement. At surgery, he was found to have a neoplastic mass in the mid-CBD involving the anterior branch of the right hepatic artery. A radical extrahepatic bile duct excision with cholecystectomy was performed. On frozen section, both the margins of resection were free of tumor. A roux-en-y hepaticojejunostomy was performed. Postoperative histopathology revealed a moderately differentiated adenocarcinoma involving the neck of the gall bladder and the CHD. Lymph nodes dissected did not show evidence of tumor. Both the surgical margins were clear. The patient is disease-free at 5 months’ follow-up.

Case 4

A 48-year-old male presented to us with obstructive jaundice 15 days. On examination, the patient had a palpable lump in the right hypochondrium. His blood examination revealed normal bilirubin levels (serum bilirubin = 1.01 mg/dl) with a CA19-9 level of 2105 units/ml. A contrast-enhanced CT of the abdomen showed an irregular thickening of the wall of the gallbladder with soft tissue density in the fundus. An MRCP revealed a stricture of the CHD just distal to the confluence as well as in the distal CBD. Diagnosed as a case of locally advanced gallbladder cancer, the patient was given four cycles of anterior chemotherapy (Gemcitabine and Cisplatinum). The MRCP that was performed after the chemotherapy showed disease regression (Figure 2a). PET CT imaging failed to show active disease. The patient was therefore considered for surgical resection. At surgery, he was found to have a neoplastic mass in the gall bladder involving the CBD with a solitary metastasis in segment 3 of the liver. A radical cholecystectomy with radical extrahepatic bile duct excision was performed. In view of no further lesions detectable on intra-operative ultrasonography, a left lateral segmentectomy was also performed (Figure 2b). A 2-duct hepaticojejunostomy had to be done owing to the right posterior sectoral duct having an anomalously low insertion in the CHD. On frozen section, all margins of the resection were free of tumor. Postoperative histopathology revealed a moderately differentiated adenocarcinoma involving the neck of the gall bladder and the CHD. Lymph nodes dissected did not show evidence of tumor. All the surgical margins were clear. The patient is disease-free at 5 months’ follow-up.

Discussion

When we analyse these four clinical scenarios, we can appreciate that possibly there are different patterns of spread in these cases. The four modes of spread are depicted in Figure 2.
disease spread. In the first patient, the lack of anatomical continuity between the two tumors seems to favor the likelihood of a truly synchronous malignancy. Synchronous gallbladder and CBD malignancies are rare [5]; however, there are increasing reports suggesting that they are more common than earlier reported, probably due to inadequate sampling of the gall bladder when performing a resection for extrahepatic bile duct malignancies. Their occurrence is seen to be approximately 5–7.4% [5,16,17] in Japan, where APBDJ is an important etiology [1–4]. This clinical entity is often confused with metatstasis from a primary elsewhere in the biliary tree. Gertsch et al. [6] have suggested that the best way to differentiate these two entities is by applying the following criteria, viz.: 1) No direct continuity between the two tumors, 2) a growth pattern typical of a primary tumor, 3) and clear histologic differences between the two tumors. These criteria, however, may not be sufficient to confirm synchronicity, especially in malignancies of the extrahepatic biliary tree. Kurosaki et al. [5] have in fact advised the mapping technique to confirm the distinctness of the two lesions.

Over the past few decades, the reasons for labeling extrahepatic biliary cancers as synchronous have been based on multifocal origin [8]. The criteria for differentiating between synchronous primaries and metastasis are still being developed [9]. Gallbladder cancer, in patients without APBDJ, does not follow the adenoma-carcinoma but rather the dysplasia in situ invasive carcinoma sequence [10,11]. Intraepithelial spread may also contribute to multifocality [9]. It is important to note, though, that this has been demonstrated to occur in only 4% of persons with papillary adenocarcinomas [18].

The second case seems best explained on the concept of field cancerization. The field cancerization theory was first introduced in 1953 by Slaughter when describing this concept in the aerodigestive tract [12]. The field cancerization theory has been used to explain the possibility of distant related primary tumors in the upper aerodigestive tract [13]. Unfortunately, the theory of field cancerization is seldom referred to in the case of malignancies of the extrahepatic biliary tree.

The biliary tree is almost exclusively exposed to concentrated bile, bile salts, and bile acids. Hence, there has to be an effect of the bile on the lining epithelium of the biliary tree and, consequently, on carcinogenesis [19]. This has been noted in patients with APBDJ. Findings that further strengthen the opinion of bile chemistry and the idea of field cancerization have been the detection of high levels of secondary bile acids (with accompanying raised biliary deoxycholates) [20] and heavy metals as contaminants (metallothionein) [21] in the bile of patients with gallbladder cancer. While it may be argued that these findings, especially the former, have not stood the test of time, there are factors in the bile that need to be studied further if we are to understand the pathogenesis of gallbladder and biliary cancer.

In the case of field cancerization, the phenotype is a result of a molecular event affecting multiple cells separately and independently of each other, or a single molecular event in a single clonal progenitor that leads to widespread clonal expansion or an alternative means of undergoing lateral spread across the mucosa [13].

The p53 gene mutations have been closely associated with determination of clonality [13]. Allelic loss or deletions at the TP53 locus (17p13) reported ranging from 58% to 92% in gallbladder cancer [14,15] have been noted at histologically normally appearing epithelium near gallbladder cancer [14]. Hori et al. [9] concluded that more studies on p53 mutations are needed in synchronous malignancies unrelated to APBDJ.

Since gallbladder cancers occur more frequently in females [22], X-chromosome inactivation studies could be used to determine clonal similarity between such synchronous tumors.

The role of epigenetics in field cancerization has been shown in the stomach [23,24], liver [25], colon [26–28], Barrett's esophagus [29], lungs [30], breasts [31], and kidneys [32]. Studies on DNA methylation in gallbladder cancer have been performed by House et al. [33]. While studying chromosome 3p, Riquelme et al. [34], too, have demonstrated a very high frequency of GBC methylation in SEMA3B (92%) and FHIT (66%). The time thus seems opportune to explore the role of epigenetics in field cancerization of gallbladder cancer.

Loss of heterozygosity is observed in at least 21 chromosomal regions in gallbladder cancer [35]. Chang et al. [15] have shown that LOH on 5q21
(APC-MCC genes; 6–66%) is an early event change, while LOH at 3p (20–52%) and 9p are related to progression in gallbladder cancer. They also showed that LOH on 13q (Rb gene, 20–30%) and 18q (DCC gene, 18–31%) is likely to be a late event and that LOH on 17p occurs in dysplasia but also increases during subsequent stages [36].

The third and fourth cases are representative of cancers spreading to adjacent tissues by local extension. The possible routes may be [11,18]: 1) Periductal connective tissue (Case 3), 2) perineural, and 3) lymphatics.

Involvement of the cystic duct and neck of the gallbladder by tumors of the mid-CBD has been well documented [11]. Similarly, tumors of the gallbladder have been shown to involve the bile duct. The possible manner of cancer spread in these four tumors is shown in Figure 3. The management algorithm for such lesions needs to be thought through carefully, keeping in mind that the aim is to achieve a complete microscopic resection for improved outcomes in these patients [37]. In circumstances where the synchronous disease has not yet metastasized to distant organs, as in case 1, and if radical simultaneous resection is feasible, it should be attempted. On the other hand, in the unfortunate situation where there is field cancerization, the options are limited. It is usually not possible to obtain complete removal of the cancer and therefore there is a limit to the advantages of radical resection.

Prognosis in such conditions depends on whether the simultaneous lesion is a metastasis or a synchronous one. Metastatic disease [38], perineural invasion [39], and involvement of cystic duct [40] have been shown to be associated with poor prognosis, whereas in the case of synchronous lesions a fairly good prognosis has been reported if a complete surgical resection of the disease is possible [5].

Taking into consideration the limitations of the present-day options of adjuvant therapy, it is essential that complete removal of the tumor should be the goal in patients capable of withstanding a major resection.

References


