



Synchronous Adeno-squamous Carcinoma of Gallbladder and Adenocarcinoma of Common Bile Duct: Twin Trouble

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Introduction

Synchronous malignancies of the gallbladder (GB) and common bile duct (CBD) are seen infrequently. Previously, most of the synchronous carcinomas were linked with an anomalous pancreatic bile duct junction (APBDJ); however, it is not always necessary now [1, 2]. It is the recurrent and chronic inflammation due to various etiologies that predispose to biliary tract cancers. The two different foci of malignancy can arise within the similar dysplastic environment as per the theory of field cancerization.

Usually, they are identified either intra- or post-operatively after cut section of the specimen. Hepato-pancreatico-duodenectomy can offer R0 resection for such dual malignancies but it has been reported in only few case series [2–4]. The prognosis of such synchronous malignancies is also grim. Here, we report a case of synchronous malignancy of the GB and CBD with different tumor biology, diagnosed intra-operatively and managed successfully with hepato-pancreatico-duodenectomy.

Case Presentation

A 45-year-old male presented to us with pain in the right upper abdomen and obstructive jaundice associated with cholestatic

features developed over 1 month. He had history of anorexia and weight loss. On examination, he was icteric and, on abdominal examination, tender gallbladder lump was palpable. Biochemical investigation revealed deranged liver function test: bilirubin—18 mg/dl; AST—138 U/L; ALT—112 U/L; ALP—388 IU/L.

Ultrasound of abdomen showed thickening in the fundus of the GB and abrupt narrowing of the CBD in the middle part with dilated intra-hepatic biliary radicals. Magnetic resonance imaging (MRI) reported ill-defined eccentric soft tissue mural thickening in the fundus of GB with abrupt focal stenosis of the middle one third of CBD (Fig. 1a, b). He had undergone endoscopic biliary drainage in view of high bilirubin and cholangitis.

Later, contrast-enhanced computed tomography (CECT) of the abdomen was done that reported mass in the fundus of GB with thickening and compression of CBD due to retropancreatic lymph nodes and with stent in situ (Fig. 1c, d). With the provisional diagnosis of locally advanced gallbladder carcinoma, he was planned for radical cholecystectomy with or without CBD excision.

Staging laparoscopy showed no distant metastasis. At laparotomy, GB fundal mass was noted with minimal liver infiltration; another mass was noted in the CBD, infiltrating into the head of the pancreas and reaching up to the neck of GB. To get R0 status, hepato-pancreatico-duodenectomy was done (Fig. 2a, b). Multiple firm lymph nodes present in the pericholedochal, the periportal, and along the hepatic artery were resected. Pancreatico-jejunostomy (PJ) was done by modified Blumgart's technique. A frozen section confirmed the negative proximal margin of the common hepatic duct below confluence and hepatico-jejunostomy was done.

His feeding jejunostomy trial feed was given on 2nd post-operative day (POD) which he tolerated well and gradually his feed was increased. He was allowed orally on 4th POD which he tolerated well. His abdominal drain was removed on 5th POD. He had mild PJ leak which was managed conservatively and he was discharged on 9th POD in stable condition.

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Fig. 1 **a** Axial T2-weighted MR image showing eccentric asymmetric thickening involving the gallbladder fundus (arrow) with hypointense sludge within the lumen; **b** 2D MRCP image showing dilated common bile duct and intra-hepatic biliary radicles with abrupt cut-off of mid-distal CBD (arrowhead); **c** axial contrast-enhanced CT showing thickening in the gallbladder fundus (arrow) with stent (dashed arrows) in the common bile duct; and **d** retropancreatic lymph node (arrowhead)



Histopathology was consistent with the intra-operative findings of dual malignancy. The tumor in the fundus of GB was composed of irregular glands lined by moderately pleomorphic cells exhibiting stratification. Along with it, nests and islands of cells exhibiting squamous differentiation were noted. On immunohistochemistry (IHC), the squamoid nests were positive for p40. Hence, the features were suggestive of adeno-squamous carcinoma of GB infiltrating serosa as well as the liver (Fig. 3a, b).

A second separate tumor was noted in the CBD invading the pancreas and reaching up to the neck of GB. The tumor was composed of small- to medium-sized glands (approximately 70% gland formation), trabeculae, small

nests, and cords separated by extensive desmoplastic stroma. Intra-epithelial biliary neoplasia was noted in the CBD. On IHC, the tumor cells were positive for CK7 and CK20. Overall, the features were consistent with moderately differentiated adenocarcinoma of CBD, biliary type (Fig. 3c, d). Lymphovascular and perineural invasion was identified. There was no anatomical continuity between the two tumors. All resection margins were free of tumor. Five out of 11 lymph nodes retrieved show tumor deposits.

He received 6 cycles of adjuvant chemotherapy (Gemcitabine with cisplatin) and at the end of a year follow-up, he has no evidence of recurrence and was doing well.

Fig. 2 **a** Intra-operative image depicting gallbladder fundus mass with minimal liver infiltration and another mass involving the common bile duct extending from cystic duct to the head of the pancreas. **b** Resected specimen of hepato-pancreaticoduodenectomy

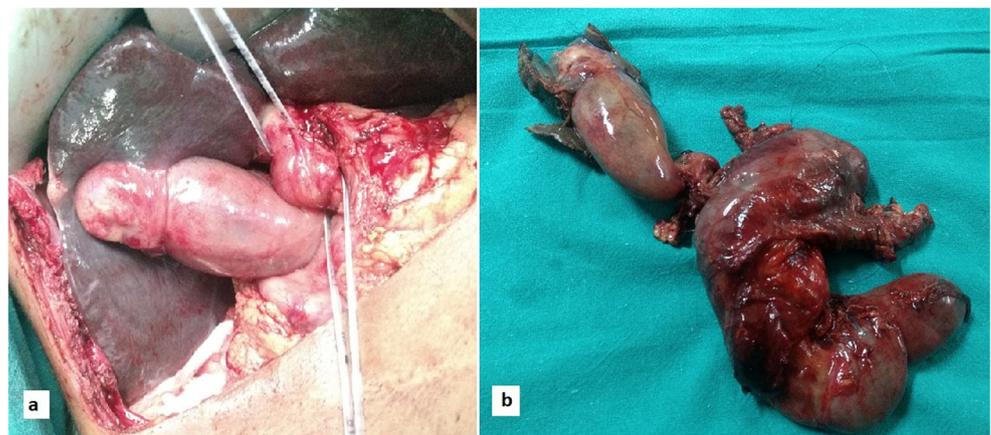
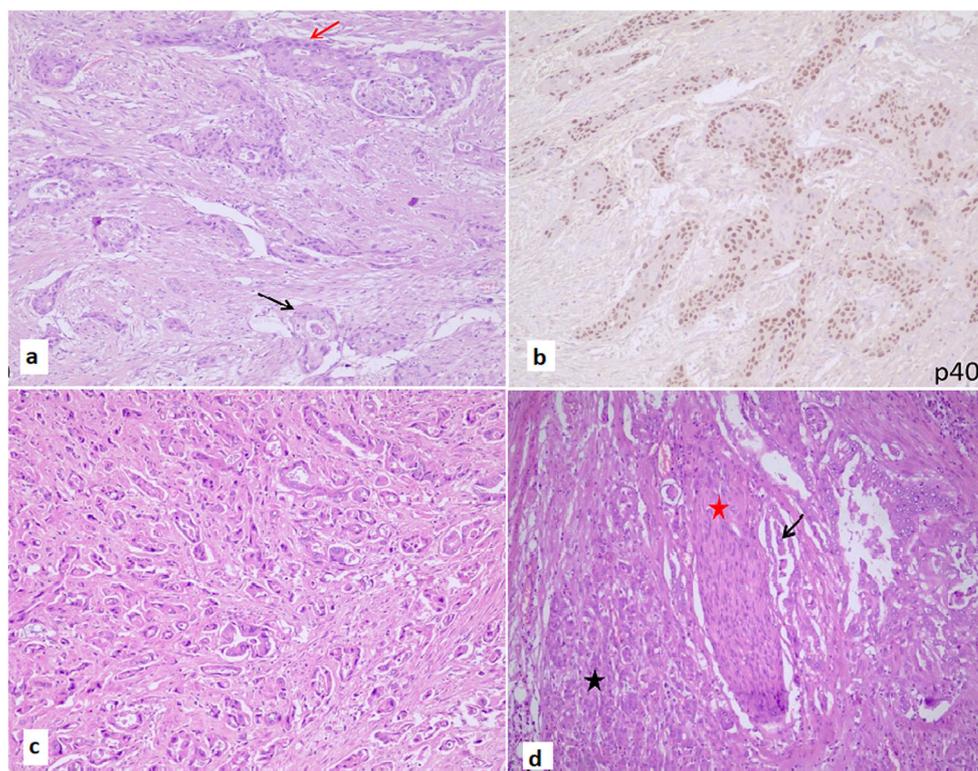


Fig. 3 Histopathology images $\times 10$. **a** Adeno-squamous carcinoma in the gallbladder fundus composed of glands (black arrow) and squamoid nests (red arrow), H&E; **b** the tumor cells in the squamoid nests are positive for p40 on IHC confirming squamous differentiation; **c** moderately differentiated adenocarcinoma of the CBD composed of malignant glands in desmoplastic stroma, H&E; **d** Panel showing CBD tumor involving pancreas (pancreas marked with black asterisk) with perineural invasion (nerve marked with red asterisk and tumor marked with black arrow), H&E



Discussion

Multicentric malignancies are known to occur in various organs of the gastrointestinal tract like the esophagus and colon. Similarly, synchronous malignancy in the extrahepatic biliary tree, i.e., gallbladder and bile duct, is diagnosed infrequently with reported incidence of $\sim 5\text{--}7.4\%$ [2]. The prognosis of such pathology depends on whether they are true synchronous lesions, locally advanced, or a result of metastatic deposit.

Gallbladder cancer (GBC) and cholangiocarcinoma usually develop in the background of chronic inflammation and follow metaplasia-dysplasia-carcinoma sequence. Increased incidence of dual malignancy was previously linked with APBDJ causing chronic irritation of the biliary tree; however, it was not absolute [1, 2]. The true synchronous malignancies usually develop in the similar epithelium with different clonality. The proposed criteria to discriminate synchronous primary from secondary deposits are that there should be no direct continuity between the two tumors, a growth pattern typical of a primary tumor, and clear histologic differences between the two tumors [5].

In our patient, all the three criteria have been fulfilled. There was a normal body of gallbladder with normal mucosa between two tumor sites. Secondly, the presence of intra-epithelial neoplasia (biliary type) in CBD along with adenocarcinoma confirmed its primary origin. Lastly, the histologic difference commented in all reports was based on the degree

of differentiation. In our case, the actual histology of both the tumors was different, i.e., adeno-squamous of GB with adenocarcinoma of the bile duct. In the current available literature, this kind of histopathological variant has been reported only once by Hayashi et al. [6].

Pre-operatively, it was diagnosed as having GBC with retropancreatic lymphadenopathy and the plan was radical cholecystectomy. Usually, dual malignancies are suspected intra-operatively or after visualizing the cut section in the immediate post-operative period. Complete surgical resection should be the goal to confirm good prognosis. Gallbladder malignancies with obstructive jaundice are usually locally advanced with low resectability rate [7]. Hepato-pancreatico-duodenectomy (HPD), i.e., performing radical cholecystectomy with pancreatico-duodenectomy, has been performed in locally advanced gallbladder cancer infiltrating the pancreas or duodenum, or with extensive retropancreatic lymphadenopathy. However, the morbidity of the procedure is high with risk of pancreatic fistula and liver failure, but it is the only option for getting microscopic negative margins.

In our case, in view of good performance status of the patient, GBC with limited liver infiltration, contained lymph nodal disease, and intra-operative suspicion of bile duct malignancy with infiltrating pancreas, HPD was performed successfully. The HPD for dual malignancies is reported in few case series with resectability rate of $14\text{--}28\%$ [2–5].

The prognosis of such dual malignancy is also very poor. The survival after doing radical resection has been variable ranging from 3 to 59 months [2–5]. Lymphovascular/perineural invasion, lymph nodal burden, and positive margin status are the important causes of early recurrence. Therefore, adjuvant chemotherapy is usually recommended to decrease the risk of distant metastasis and increase the survival, but the actual evidence is lacking.

To conclude, resection of synchronous malignancies of GB and CBD is feasible. Pre-operative suspicion of dual malignancy can avoid intra-operative misadventure. HPD can be considered depending on the general condition of the patient and contained disease.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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