Synchronous Gall Bladder and Bile Duct Cancer: A Short Series of Seven Cases and a Brief Review of Literature

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Background: **Simultaneous presence of cancer in the gall bladder and in the biliary tree could be due to local spread, metastases, *de novo* multifocal origin, or as part of a field change. In the past, such an association has been described in patients with anomalous pancreatico-biliary ductal junction.** ***Aims:*** **We studied seven consecutive patients with simultaneous gall bladder and bile duct malignancy with a view to identify the best way to treat them, and if possible to hypothesize the etiopathogenesis.** ***Methods:*** **Over a period of 24 months, there were seven cases, with synchronous gall bladder and extra-hepatic bile duct cancer.** ***Results:*** **None of our patients had anomalous pancreatico-biliary ductal junction. Three patients were found to have inoperable disease, three other underwent curative resection, and one patient had a complete response to chemotherapy. Herein, we describe these patients and our lessons learnt from these patients with synchronous bile duct and gall bladder cancer. Of the seven patients, we were able to complete a curative resection in three patients, and the three patients were found to have inoperable disease. One patient had an excellent response to chemotherapy.** ***Conclusion:*** **Thus aggressive therapy in such patients with gall bladder cancer may be warranted in select cases. Also, the gall bladder specimens in patients undergoing surgery for cholangiocarcinoma should be analyzed in detail to identify foci of dysplasia or change in the epithelium. The pathogenesis may be due to a common field change in the biliary epithelium.** **(J Clin Exp Hepatol 2017;7:115–120)**

Gall bladder cancer occurring at the same time along with cancer of the extra-hepatic bile ducts (cholangiocarcinoma) is a rare occurrence,[1] but increasing reports suggest that this may be more common than previously believed, probably due to inadequate sampling of the gall bladder specimen when resected along with extra-hepatic bile ducts for cholangiocarcinomas. The occurrence is believed to be approximately 5–7.4%[2–4] in Japan, where abnormal pancreato-biliary ductal junction (APBDJ) is an important association.[5,6] The possible explanations for such an occurrence could range from the rare synchronous malignancies to local peri-neural, lymphatic or vascular invasion, or to metastasis. This clinical entity may often be confused with metastatic spread from a primary elsewhere in the biliary tree.

Keywords: gall bladder cancer, cholangiocarcinoma, synchronous, field cancerization, obstructive jaundice, metastasis

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Abbreviations: APBDJ: abnormal pancreato-biliary ductal junction; CBD: common bile duct; CT: computerized tomography; PET: positron emission tomography

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Kurosaki et al. and Hori et al. suggested in 2006 that an APBDJ was not required in double cancers on the biliary tract.[2,7] Extrahepatic biliary cancers are labeled as synchronous based on a multifocal origin. Criteria for defining synchronous primary cancer and differentiating from metastatic disease are still being developed. Gallbladder cancer does not usually follow the adenoma-carcinoma but rather the dysplasia in situ invasive carcinoma sequence.[1] Therefore, it may become possible for two different foci of malignancy to arise within the same dysplastic environment. The entire biliary epithelium is exposed to biliary carcinogens that may arise due to changes in the nature of bile. The theory of field cancerization was described in 1953 by Slaughter et al. for the aerodigestive tract.[8] The same field cancerization may apply to biliary epithelium, especially in patients with APBDJ. In other patients with double cancers, the cause for a change in the mucosa and dysplasia will need to be investigated. Carcinomas of the pancreas, gallbladder, extrahepatic bile ducts, and ampulla have a common embryonic cellular origin, differentiation pattern, mucosal histology, and population-related tumor development indicating a field effect in those developing malignancy. Also, the genetic profile of these malignancies, p53 mutations, and K-ras mutations are common to gall bladder, biliary, ampullary, and pancreatic cancers. Gemcitabine and the pyrimidine analog 5-fluorouracil have also been shown to be associated with improvement, albeit marginal improvement, in survival in the biliopancreatic cancers. Thus these cancers behave in a similar way, occur

in the same environment that is exposed to bile, and may share the same genetic origins.

METHODS

Seven consecutive patients with synchronous malignancy of the gall bladder and the extra-hepatic bile ducts were included in this brief review. Five consecutive patients with synchronous gall bladder as well as bile duct malignancy treated at Post-graduate Institute of Medical Education and Research, Chandigarh, and one patient with similar presentation at B.J. Medical College and Sassoon General Hospital, Pune, and one patient treated at Jehangir Hospital, Pune were included in the analysis (Table 1).

Patient Characteristics

Of these seven patients, five were female and two male. Five patients had gall stones, but only two patients had a history of biliary colic. Five patients presented with obstructive jaundice, and two patients were operated without jaundice. Of the five patients with jaundice, one patient presented as Mirizzi syndrome, and no tumor was detected on pre-op imaging. Four other patients had jaundice. Two patients were diagnosed on pre-operative imaging as cholangiocarcinoma in the common hepatic duct (hilar cholangiocarcinoma, Bismuth type 2 and 3); in whom, the gall bladder cancer was detected at surgery. All the patients underwent pre-operative evaluation with tri-phasic computerized tomography (CT) scan of the abdomen and pelvis, and had a chest X-ray. Positron emission tomography (PET)-scan was not done as a routine in these patients, though one patient had a PET scan done before she was referred to us. CT scan did not demonstrate vascular invasion in any of the patients who were offered primary surgery. One patient was diagnosed to have gall bladder cancer extending to the common hepatic duct, who had a second tumor in the common bile duct (CBD) at surgery. One patient presented with metastatic hilar cholangiocarcinoma with obstructive jaundice, who had a near complete response to chemo-radiation, and subsequently was found to have a T1a malignancy of the fundus of the gall bladder.

The two patients, who presented without jaundice, were a female who was referred for biliary colic, and was found

Table 1 Clinical Profile of all the Patients in the Study.

Sr. no.	Age/sex	Anatomy of double cancer	GSD	APBDJ	Jaundice	Surgery
1.	37 F	Hilar Cholangiocarcinoma + gall bladder lesion (6 mm, discontinuous, near the cystic duct)	–	–	+	Extended cholecystectomy with radical resection of extra-hepatic bile ducts + hepatico-jejunostomy
2.	61 F	Presented with Ca GB, and intra-op detection of 10 mm growth in supra-duodenal CBD (non-obstructing, encasing the portal vein and hepatic artery + celiac nodes)	+	–	–	Inoperable, hence bile duct stented, and referred for palliative chemotherapy
3.	43 M	Operated for Mirizzi syndrome; found to have a 13 mm growth in the GB fundus (pre-op imaging diagnosed at multiple GB calculi) as well as a discontinuous growth in the infra-cystic CBD (hepato-duodenal vessels involved + celiac and aortocaval nodes)	+	–	+	Inoperable. The obstructing stone was removed, and the CBD was stented (patient had a fatal cardiac event on post-op day 2)
4.	63 F	Klatskin tumor (Bismuth type 2) detected to have a discrete 8 mm growth in the fundus of the gall bladder	–	–	+	Extended cholecystectomy with radical resection of the extra-hepatic bile ducts + hepaticojejunostomy.
5.	51 F	Operated for Ca GB, found to have non-obstructing growth in the retro-duodenal CBD, with aortocaval nodes, and celiac nodes	+	–	–	Inoperable, CBD was stented and referred for palliative chemotherapy
6.	55 M	Operated for Ca GB causing obstructive jaundice, found to have a second growth in the retro-duodenal CBD involving the duodenum and pancreatic head	–	–	+	Extended cholecystectomy + pancreato-duodenectomy (Whipple's operation) [fatal cardiac event on post-op day 4]
7.	41 F	Stg 4 cholangio Ca with retroperitoneal nodes. Stent + chemo + radiation—complete radiological response to CT + RT	–	–	+	Cholecystectomy—after CT + RT no residual disease found at Ex-lap. Histology shows T1b cancer at fundus of GB

Clinical details of the patients included in the study. The eventual outcomes and surgery performed are mentioned in the last column.
GSD, gall stone disease; APBDJ, anomalous pancreatico-biliary ductal junction; CaGB, carcinoma gall bladder; CT, chemotherapy; RT, radiotherapy; GB, gall bladder; CBD, common bile duct.