

Synchronous cholangiocarcinoma and gallbladder cancer: A rare presentation

Puppala Venkata Sagar, Kanchustambam Subba Rao

ABSTRACT

Introduction: Synchronous biliary tree and gallbladder cancers are rarely encountered and reported in the literature. In this article, we report an extremely rare presentation of a patient with distal common hepatic duct (CHD), proximal common bile duct (CBD) and gallbladder cancer associated with anomalous pancreaticobiliary duct junction (APBDJ) as primary tumors. **Case Report:** A 40-year-old male referred to us with RUQ pain, fever, jaundice and pruritis since two weeks. PET-CT showed hypermetabolic polypoid mass in the fundus of gallbladder and a periportal node. ERCP was done but guide wire could not be passed beyond mid CBD. The findings were neoplastic mass in fundus of the gallbladder with pericholedochal lymphadenopathy. There was another neoplastic mass in the CBD. An extended cholecystectomy with extrahepatic CBD excision with a pancreaticoduodenectomy with radical lymphadenectomy was performed. Intra-operative ultrasonography was done to rule out other lesions in the pancreas and liver. Histopathological examination revealed well differentiated adenocarcinoma of gallbladder

and adenocarcinoma of proximal CBD and distal CHD, staging pT2 pN0 pMx. **Conclusion:** Synchronous extra hepatic and gallbladder tumors are extremely rare, their etiopathogenesis has not been properly understood and defined. Biliary cancers with PBM are thought to develop multicentrally, due to the effect of pancreatic juice reflux on the mucosa of the biliary tract.

Keywords: Adenocarcinoma, Anomalous pancreaticobiliary maljunction, Biliary tree, Synchronous

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INTRODUCTION

Cholangiocarcinoma is a malignant neoplasm arising from the epithelium of the biliary tract, histologically described by Durand-Fardel in 1840. Cholangiocarcinomas are anatomically classified as originating from the intra- and extrahepatic biliary epithelium [1]. Extrahepatic cholangiocarcinomas are further separated into upper-third or perihilar (including the confluence of the right and left biliary ducts) tumors; middle-third tumors; and distal bile duct tumors. About 5% of cholangiocarcinomas may be multifocal [2]. Different histologies, tumor locations, and treatment techniques all affect the ultimate outcome. In this article, we report an extremely rare presentation of a patient with

distal common hepatic duct (CHD), proximal common bile duct (CBD) and gallbladder cancer as primary tumors.

CASE REPORT

A 40-year-old male presented with a two-week history of right upper quadrant pain, fever, history of weight loss exceeding 20 pounds. Initial evaluation revealed obstructive jaundice with intractable pruritus. Physical examination was significant for scratch marks, jaundice in the absence of hepatomegaly or splenomegaly but there was palpable globular mass probably distended gallbladder. Murphy's sign was negative.

Diagnostic work-up

Initial laboratory data revealed a white blood cell count of 5,280 mm³, hemoglobin concentration of 10g/dL, platelet count of 286,000 mm³, total bilirubin level of 16.7 mg/dL (direct bilirubin level = 13 mg/dL), albumin level of 3.2 g/dL, aspartate aminotransferase level of 119 U/L, alanine aminotransferase level of 99 U/L, alkaline phosphatase level of >700 U/L, γ -glutamyl transpeptidase level of 374 U/L, and lactate dehydrogenase level of 783 U/L. The remainder of the chemistry panel, renal function tests, and electrolytes were normal. The patient had normal coagulation studies, a prothrombin time of 13.2 seconds, a partial thromboplastin time of 34.6 seconds, and an international normalized ratio of 1.12. His tumor markers revealed a CA19.9 level of >500 U/mL.

A ultra sound revealed distended gallbladder with fundal mass and dilated intra hepatic biliary radicles. A CT scan of the patient's abdomen revealed evidence of moderate-to-severe, right and left intrahepatic ductal dilatation; a mass in the fundus of gallbladder 3–4 cm, portacaval lymph node compressing CBD and pancreatic head; and no evidence of intrapancreatic duct dilatation. A work-up for metastatic disease, which included a PET scan revealed (1) hypermetabolic polypoidal mass in fundus of gallbladder, (2) Hypermetabolic periportal node- metastatic nature (Figure 1, 2, 3). Endoscopic retrograde cholangio-pancreaticogram was attempted but it was failed as the guide wire couldn't be progressed in the common bile duct (Figure 4). A differential diagnosis of periportal node obstructing CBD or malignant stricture was made.

Treatment

The patient planned radical cholecystectomy and periportal nodal dissection. Right Hockey stick incision was given and it was found that there was a neoplastic hard mass in fundus of the gallbladder with pericholedochal lymphadenopathy. There was another neoplastic mass in the Common bile duct (Figure 5). Portal vein was adherent to the common bile duct (Figure 6). Intra-operative ultrasonography was done to rule out other lesions in the pancreas and liver. Common bile

duct mobilization was done from the portal vein and hepatic artery. Extended Duodenum Kocherization was done. Duodenum was mobilized till jejunum. Superior mesenteric vein dissection was done from the pancreas. Finally an extended cholecystectomy including liver segment 4b and 5, along with excision of extrahepatic common bile duct with a pancreaticoduodenectomy and radical lymphadenectomy was performed. Finally hepaticojejunostomy and pancreaticojejunostomy has been illustrated in Figure 6. Final resected specimen (Figures 7–9) grossly showed the following findings:

- Gallbladder with nodular exo-phytic tumor having a broad based attachment spread over a base of about >4–5 sq. cm with a nodular surface
- Cystic duct is normal smooth
- Irregularly elliptical/ oval tumor mass, with nodular surface, obstructing the CHD and Proximal CBD, causing dilatation of both tubes.
- The distal CBD and proximal CHD are free from deposits, and showed normal surface
- No deposits seen in attached piece of liver, pancreas, pancreatic duct, and distal D and J
- The other part of the specimen i.e., nodal mass surrounding HA, para-aortic LNs – are grossly red brown in colour, no macroscopic evidence of deposits.

The histological features observed were as follows: (Figures 10–17)

- Tumor: Well differentiated adenocarcinoma
- The tumor histomorphology was similar in both locations, i.e., in gallbladder and Common Hepatic Duct (CHD)+Common Bile Duct (CBD) lesions
- Margins: The tumor mass was seen invading up to the muscle layer, however, not invading the serosa of the gallbladder. The second mass in the CBD and CHD also showed invasion up to the muscular layer, without any invasion noticeable in the serosa
- The gallbladder mucosa near to the tumor and CBD+CHD mucosa showed dysplastic changes
- The cystic duct, LNs at cystic duct, the attached liver, head of pancreas, distal CBD, proximal CHD were free from tumor deposits
- The nodal mass surrounding HA, paraaortic LNs, nodal mass all were free from tumor deposits

No lymphovascular, perineural deposits were detected.

Histological Diagnosis and staging:

- Synchronous well differentiated adenocarcinoma of gallbladder, (intestinal type, multi-focal adenocarcinoma), with 2nd focus in distal CHD & proximal CBD- (pT2)
- Invasion of the tumor seen up to the muscular layer, no deposits/ penetration of the serosa seen
- The distal CBD, proximal CHD, attached portion of liver, head of pancreas, pancreatic duct, ampulla of Vater, duodenum jejunum are free



Figure 1: PET-CT scan sagittal section showing hyperechoic mass in the fundus of gallbladder and intrahepatic biliary dilatation.

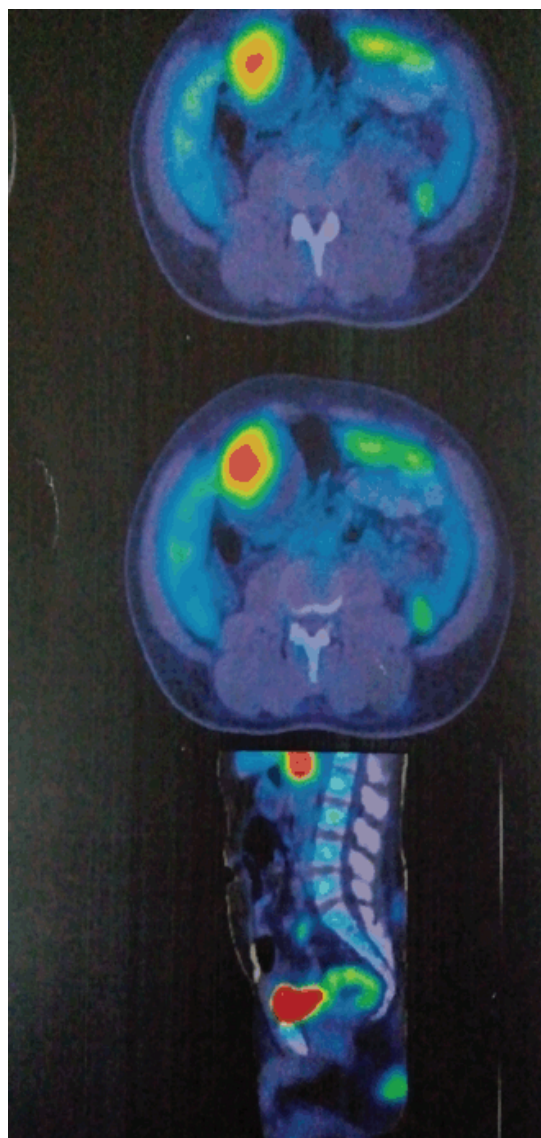


Figure 3: PET-CT scan showing high SUV value uptake in gallbladder fundus.



Figure 2: PET-CT scan axial section showing hyperechoic mass in gallbladder.

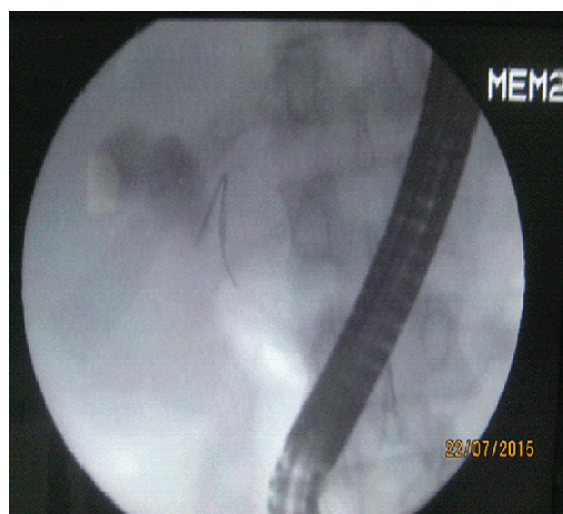


Figure 4: Endoscopic retrograde cholangiogram showing a guide wire which is getting coiled in the distal common bile duct due to a malignant stricture or perinodal mass obstructing the common bile duct.

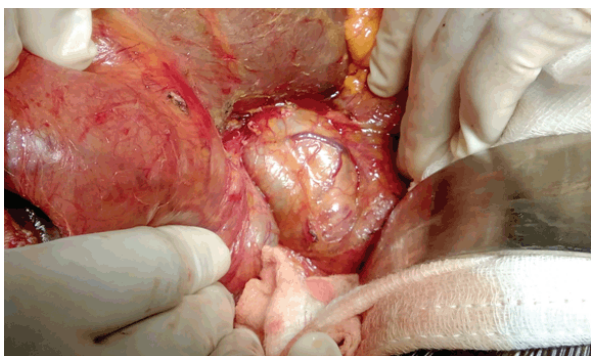


Figure 5: Intraoperative finding showing distended gallbladder and dilated common bile duct with mass.

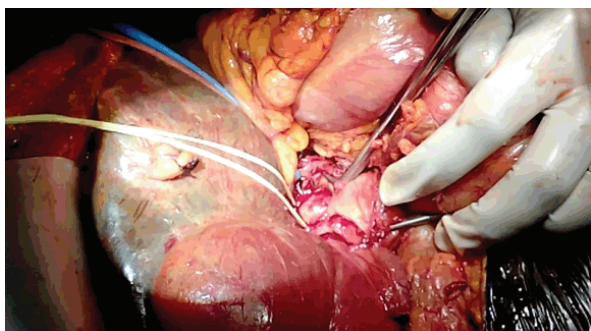


Figure 6: Intraoperative finding of portal vein adherent to common bile duct.



Figure 7: Final Anastomosis after resection showing hepaticojejunostomy and pancreaticojejunostomy.



Figure 8: Resected specimen showing gallbladder with mass and wedge resected liver and dilated common bile duct with mass, duodenum with head of pancreas and proximal jejunum.

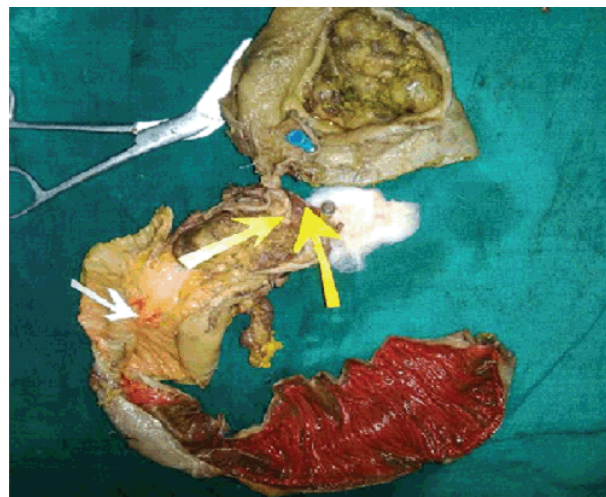


Figure 9: Specimen (cut section) showing mass arising from fundus of gallbladder and mass in common bile duct. There is an anomalous pancreaticobiliary duct junction small in length and diameter.

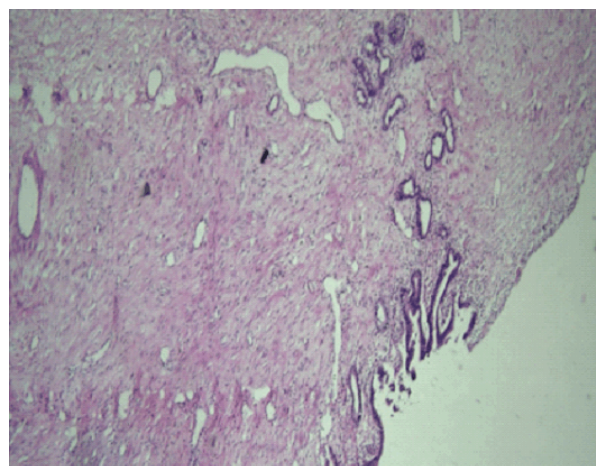


Figure 10: Histological view of gallbladder mucosa with dysplasia.

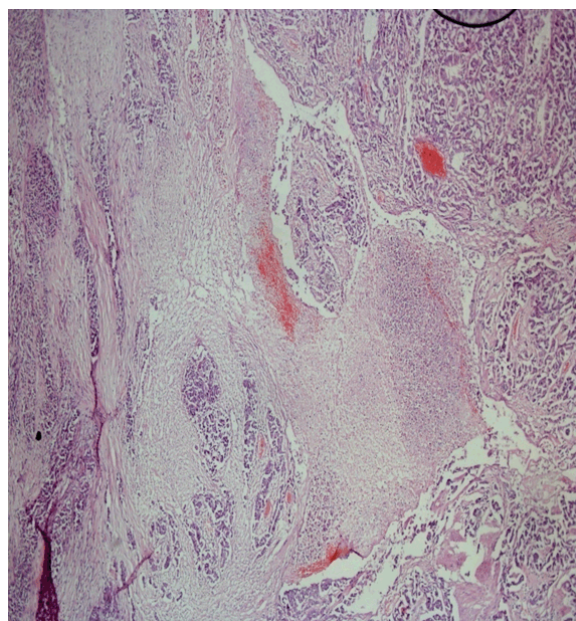


Figure 11: Microscopic view of gallbladder mass, 5x.

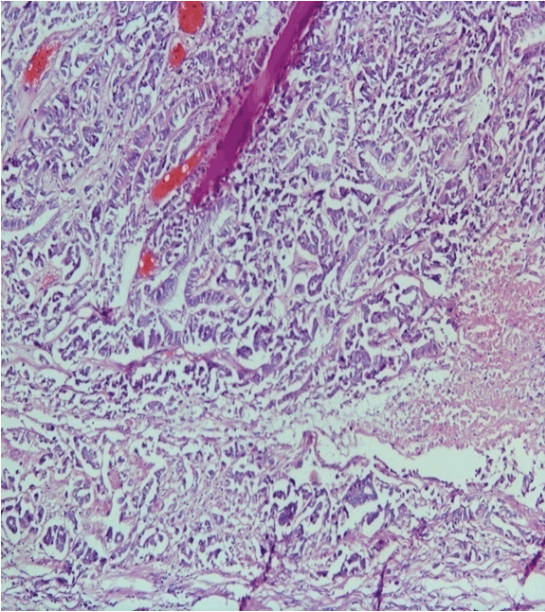


Figure 12: Histological view of gallbladder mass, 10x.

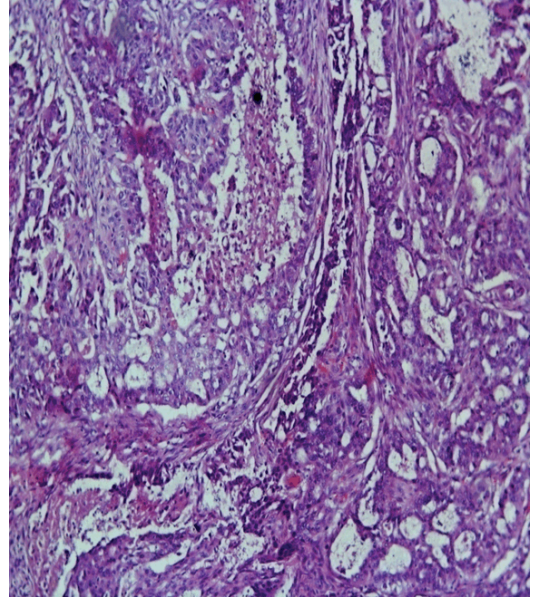


Figure 15: Histological view of common bile duct mass, 10x.

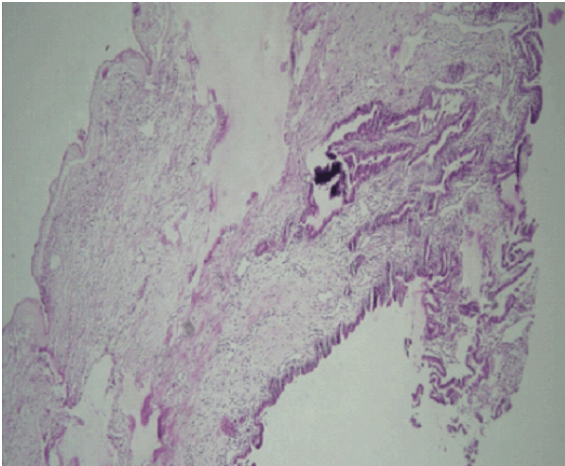


Figure 13: Histological view of common bile duct mucosa showing dysplasia.

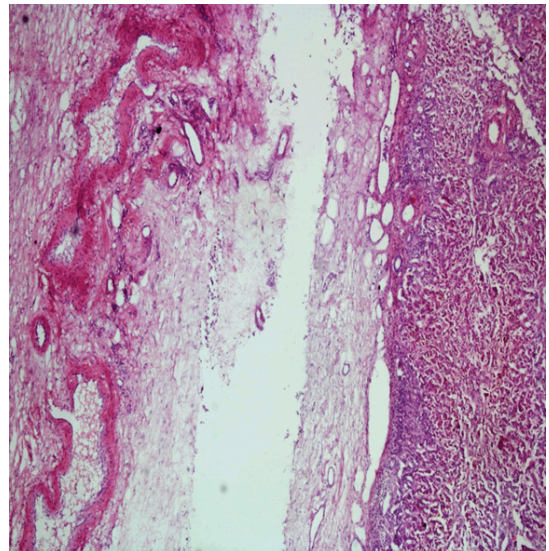


Figure 16: Serosa of common bile duct and pancreas 5x.

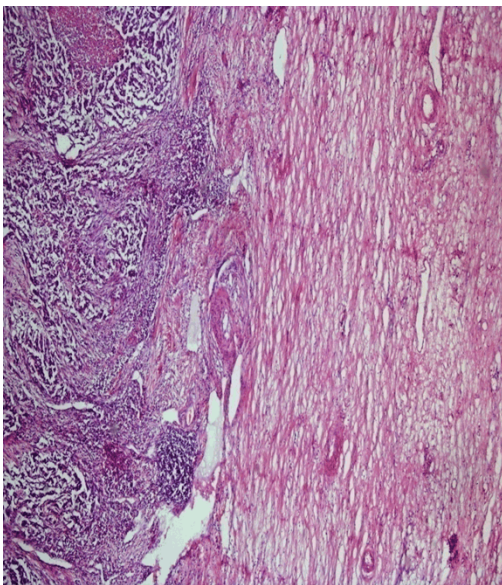


Figure 14: Microscopic view of common bile duct mass, 5x.

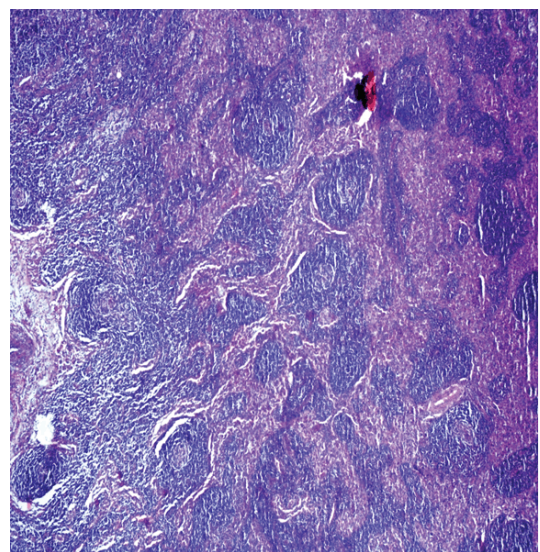


Figure 17: Lymph node at cystic duct.

from tumor deposits

- All the LNs sent from different locations are free from deposits, (pNo)

Histological staging, (TNM): pT2, pNo, pMx.

Postoperative period was uneventful and patient discharged from hospital in eight days after surgery.

At 6th month follow-up abdominal ultrasound was done twice and was found to be normal.

DISCUSSION

Synchronous extra hepatic and gallbladder tumors are extremely rare, their etiopathogenesis has not been properly understood and defined. Fujii et al. reported that 62.5% of synchronous double cancers and 100% of metachronous double cancers of the biliary tract were associated with anomalous pancreaticobiliary duct junction but not established in this patient. Biliary cancers with anomalous pancreaticobiliary duct junction are thought to develop multilocally, due to the effect of pancreatic juice reflux on the mucosa of the biliary tract. However, there are increasing reports suggesting that they are more common than earlier reported, probably due to inadequate sampling of the gallbladder when performing a resection for extrahepatic bile duct malignancies. Their occurrence is seen to be approximately 5–7.4%, in Japan, where anomalous pancreaticobiliary duct junction is an important etiology. This association with APBDJ is not an absolute necessity or rule

Gertsch et al. have suggested that the best way to say synchronicity by applying the following criteria, viz.,

- No direct continuity between the two tumors,
- A growth pattern typical of a primary tumor, 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. have in fact advised the mapping technique to confirm the distinctness of the two lesions.

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

While studying chromosome 3p, Riquelme et al., too, have demonstrated a very high frequency of gallbladder cancer methylation in SEMA3B (92%) and FHIT (66%). The time thus seems opportune to explore the role of epigenetics in field cancerization of gallbladder cancer.

By newer imaging technique, intraductal ultrasonography, has the ability to visualize the bile ducts and evaluate the degree of nodal involvement

[3]. Cholangiographic techniques, such as magnetic resonance cholangiography, endoscopic retrograde cholangiopancreatography (ERCP), and percutaneous transhepatic cholangiography (PTC), are used for detailed bile duct imaging and (in combination with magnetic resonance angiography) accurate staging, as well as evaluation of vascular invasion by the tumor [2]. ERCP demonstrates the site of obstruction by direct retrograde dye injection and excludes ampullary pathology by endoscopic evaluation. Brush cytology, biopsy, needle aspiration, and shave biopsies via ERCP can provide material for histologic studies. Palliative stent placement relieves biliary obstruction and can be performed at the time of evaluation. In proximal lesions, in which both the right and left hepatic ducts are obstructed, PTC may provide access to the lesion, drainage of the obstruction, and a means of obtaining material for cytologic studies [3, 4, 5].

Surgical resection gives the better outcome and is associated with a survival benefit, especially when resection margins are free from cancerous infiltration [6, 7]. Adjuvant radiotherapy is given to improve local tumor control after complete resection and has a variable effect on the overall survival rate. Several series have shown an increase in the duration of median survival, from 8 months with surgery alone to more than 19 months with postoperative irradiation. Intraluminal brachytherapy and intraoperative radiotherapy have provided a survival advantage and significant palliation over stent placement or bypass surgery alone in patients with medically inoperable or unresectable tumors [8, 9]. The rate of margin-negative resection increases to 100% with preoperative chemoradiation, compared with 54% without preoperative chemoradiation therapy, suggesting that preoperative chemoradiation therapy produces a significant antitumor response and improvement in tumor-free resection margins [10, 11].

Objective response rates with 5-fluorouracil (5-FU) and 5-FU-based combination therapies range from 0% to 34%, and median survival is less than 6 months. Higher response rates are seen with either infusional administration of 5-FU or leucovorin-modulated 5-FU therapy, but whether such treatment translates into better survival is unclear. Gemcitabine (Gemzar) combined with cisplatin as first-line chemotherapy has been evaluated as well. Overall response rates with gemcitabine alone range from 13–60%, but median survival is only 8 months [2]. More favorable results are seen when gemcitabine is combined with cisplatin, capecitabine (xeloda), irinotecan, or oxaliplatin (eloxatin) [12, 13, 14]. In two representative published studies with a total of 72 patients (60 with cholangiocarcinoma), the overall objective response rates were 28% and 35%, and median survival was 9 and 11 months, respectively [12, 15]. In a group of 33 untreated patients with advanced biliary cancer and a good performance status, using gemcitabine (1,000 mg/m²) on day 1 every 2 weeks and oxaliplatin (100 mg/m²) on day 2, resulted in a response rate of 36% and a median

overall survival of 15.4 months. The patients generally tolerated the regimen well [7, 13].

Orthotopic liver transplantation is considered for some patients with proximal tumors who are not candidates for resection because of the extent of tumor spread in the liver [12]. Liver transplantation may have a survival benefit over palliative treatments, especially for early-stage tumors. A five-year survival rate greater than 80% has been seen in selected transplant patients [8]. It is essential that complete removal of the tumor should be the goal in patients capable of withstanding a major resection.

Common risk factors for occurrence of synchronous carcinoma in biliary tree are gallstones disease, anomalous pancreatic bile duct junction (APBDJ), hepatobiliary infections by parasites, (liver flukes). The possible explanations for synchronous occurrence could be local spread, metastasis, multifocal origin. The majority of cases of synchronous malignancies reported are from Japan, where malignancies are usually associated with anomalous pancreatic bile duct junction (APBDJ). This association with APBDJ is not an absolute necessity or rule. There are no very well approved criteria for differentiating between “synchronous primaries and metastasis” these are still being developed. The good method of differentiating the above possibilities are, by applying the following criteria,

- No direct continuity between the two tumors being described
- A growth pattern, in all the ways esp. histological appearance criteria, typical of a primary tumor
- Presence of predisposing factors in the site involved

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. The p53 gene mutations have been closely associated with determination of clonality. Allelic loss or deletions at the TP53 locus (17p13) reported ranging from 58–92% in gallbladder cancer more studies on p53 mutations are needed in synchronous malignancies unrelated to APBDJ.

CONCLUSION

Both lesions were morphologically, histologically similar, and occurred in close proximity of the biliary tree. The gallbladder mucosa and CBD mucosa showed “dysplasia”, indicating field cancerization – giving chance for occurrence of multiple primary tumors. It is concluded as “synchronous multifocal origin”.

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Author Contributions

Puppala Venkata Sagar – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Kanchustambam Subba Rao – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None

Consent Statement

Written informed consent was obtained from the patient for publication of this case report.

Conflict of Interest

Authors declare no conflict of interest.

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