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IP Journal of Diagnostic Pathology and Oncology

Journal homepage: <https://www.jdpo.org/>

## Case Report

# Multifocal biliary carcinoma; whether synchronous or metastatic: A need to conquer

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### ARTICLE INFO

#### Article history:

Received 20-01-2023

Accepted 21-04-2023

Available online 22-06-2023

#### Keywords:

Multiple synchronous

### ABSTRACT

Multiple synchronous primary carcinoma involving gall bladder, liver and common bile duct are rare and difficult to differentiate with hepatic and extrahepatic bile duct metastasis from single primary. Radiological features, molecular landscape, and even integrated mutational profiling are not of much help. We describe a case of 48-year-old male who presented with jaundice and follow up CT scan raised the suspicion of gall bladder carcinoma with hepatic metastasis. Peroperative frozen section examination revealed adenocarcinoma with involvement of cystic duct margin; however revised common duct margin was free from tumor invasion. Final histopathology on resected gall bladder revealed multifocal adenocarcinoma, while histomorphology of hepatic nodule was consistent with cholangiocarcinoma. Common bile duct a one focus had also revealed adenocarcinoma while cut margins were negative for malignancy. In view of different morphology of gall bladder and hepatic tumor, no continuity of three tumors and single large, firm, non umbilicated hepatic nodule, diagnosis of multiple synchronous carcinoma was suggested.

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## Introduction

Incidence of multiple primary cancer are rare and varies between 0.734% to 11.7%.<sup>1</sup> It is defined as more than one synchronous or metachronous cancers in the same individuals if arising in different sites and/or are of a different histology or morphology.<sup>2</sup> Metachronous second malignancy seen in long term follow up are easy to manage, however synchronous multiple primaries are always been a diagnostic and therapeutic challenge. Here in we report a case of multiple synchronous primaries involving gall bladder, liver and common bile duct.

## Case Report

A 48-year-old male had come as known case of Carcinoma gall bladder. Patient had no known family, genetic or chronic disease history. On examination his vitals were normal. Routine investigations revealed deranged liver function. Serum Bilirubin was 8.69 mg/dL, Alkaline phosphate 1115U/L, SGOT 131I U/L, and SGPT 141 IU/L. Serum albumin and globulin, renal function test, complete blood count, coagulation profile, blood sugar, HbA1C were within normal range. CA 19.9 was markedly raised >1000 U/ml. He was planned for Radical cholecystectomy with Roux-En-Y Hepaticojejunostomy. Peroperative frozen section from cystic duct margin and liver nodule was positive for malignancy (adenocarcinoma). Second frozen section was from 4.0 cm long resected common bile duct. Here both the cut margins were free from tumor invasion. Final histopathology on resected specimen [Figure 1a,b] revealed

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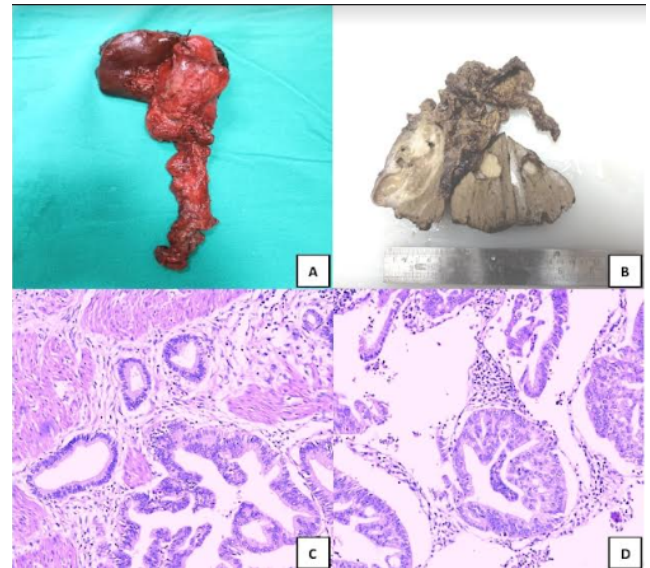
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multifocal gall bladder adenocarcinoma with prominent xanthogranulomatous changes. Infiltrating atypical glands are seen in the muscularis propria of fundus, neck and cystic duct 'well differentiated adenocarcinoma T1b' [Figure 1c]. Neck and cystic duct mucosa also revealed biliary intraepithelial neoplasia [Figure 1d]. Separate firm, well circumscribed nodular mass in liver revealed adenocarcinoma with anastomosing glands lined by low cuboidal to flat epithelium separated by desmoplastic stroma [Figure 2a]. Common bile duct at one focus revealed invasive adenocarcinoma involving wall of the bile duct and adjacent fat while perineural invasion was seen at other areas [Figure 2c,d]. Both the proximal and distal cut margins were free from invasive carcinoma. Lymph node at level 8A and 12 were positive for metastatic cancer (3/10). As the tumor was not continuous to gall bladder carcinoma [Figure 2b] and each growth is typical to respective cancer a diagnosis of multifocal biliary carcinoma was made with possibility of synchronous multiple primary cancers was suggested. Patient had many poor prognostic factors; multiple cancer foci, lymph node metastasis, cystic duct involvement, and perineural invasion, therefore referred to department of Medical Oncology for further management and tumor blocks were sent for molecular testing.

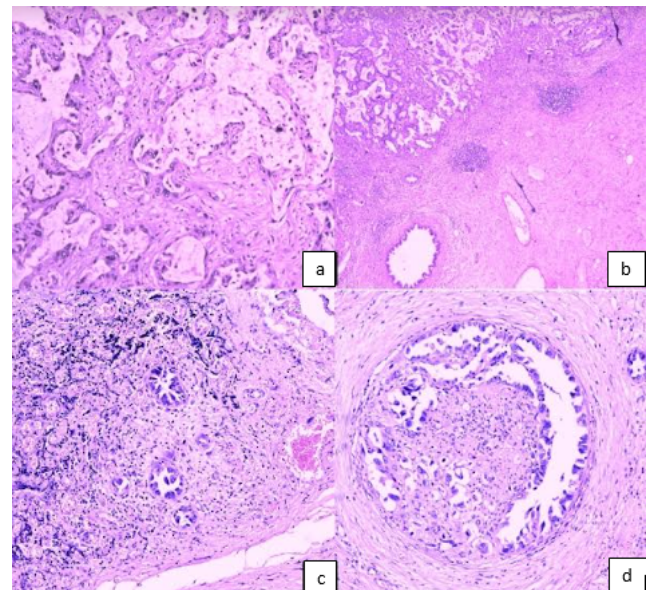
## Discussion

Multifocal gall bladder carcinoma, along with cancer of intrahepatic and extrahepatic bile duct (Cholangiocarcinoma) raises two possibilities whether it is multiple synchronous carcinomas or metastatic foci of one primary tumor. Lymph node metastasis and prominent perineural invasion favours later while several points are in favour of multiple synchronous malignancies:

1. There is no continuity between the three tumors.
2. Growth pattern and histology of intrahepatic nodule is different from gall bladder and extrahepatic bile duct carcinoma. Here atypical cuboidal cells are forming small tubular or anastomosing glands (ductal plate malformation like pattern) typical of small duct intrahepatic cholangiocarcinoma. In gall bladder and extrahepatic bile duct it is well differentiated adenocarcinoma.
3. Intraepithelial biliary neoplasia of neck and cystic duct and extrahepatic bile duct favours dysplasia, carcinoma in situ and invasive carcinoma sequences at multiple foci.
4. Hepatic nodule is single, firm and well circumscribed with no central umbilication or areas of necrosis.
5. Wide spread xanthogranulomatous changes in gall bladder favour metaplasia-dysplasia- carcinoma sequence due to changes in bile milieu.



**Fig. 1:** a: Resected specimen shows portion of liver, gall bladder and cystic duct; b: Cut surface shows thickened gall bladder wall with areas of cystic softening and a firm growth at neck region; c: Glands infiltrating muscularis propria of gall bladder at fundus, H&E, x20; d: Intraepithelial biliary neoplasia at neck region, H&E, x20.



**Fig. 2:** a: Liver nodule shows anastomosing glands lined by atypical low cuboidal to flat epithelium surrounded by abundant desmoplastic stroma, H&E, x20; b: with no continuity with surrounding gall bladder, H&E, x10; c: Common bile duct at serosal aspect shows infiltrating atypical glands; d: and perineural invasion at other areas, H&E, x40.

Similar diagnostic criteria were also adopted in previous studies.<sup>3–6</sup>

Synchronously occurring double cancers involving Gall bladder and bile duct are rare and usually associated with Pancreaticobiliary maljunction [PMB] owing to the influence of pancreatic juice reflux on the mucosa of entire biliary tract.<sup>7</sup> Here mixing of pancreatic juice with bile lead to activation of bile salts and changes in bile chemistry. Prolonged exposure of hyper concentrated bile also has been shown carcinogenic potential to entire biliary tree “field cancerization”.<sup>5</sup> Thus factors in the bile itself need to be further studied to know the pathogenesis of multifocal biliary carcinoma.

There are no specific clinical features or radiological findings which can differentiate multiple synchronous occurring malignancies from metastatic disease from single primary. Bile duct carcinoma are morphologically, immunophenotypically and biologically similar to gall bladder carcinoma. Molecular profiling p53 and K-ras are also common in both gall bladder and bile duct malignancy.<sup>3</sup>

Thus In the absence of PMB the double cancer raises a question whether it is independent primary cancer or metastatic foci from a single tumour with perineural or lymphovascular invasion.

## Conclusion

Because of low incidence of synchronous gall bladder carcinoma and cholangiocarcinoma, lack of experience, no obvious radiological features and non specific tumor markers a stringent diagnostic strategy should be evolved for diagnosis, as both the categories are prognostically different.

## Conflict of Interest

None.


## Source of Finding

None.

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**Cite this article:** Shukla A, Naqvi FS, Chaudhary S. Multifocal biliary carcinoma; whether synchronous or metastatic: A need to conquer. *IP J Diagn Pathol Oncol* 2023;8(2):117-119.