J Gastrointest Canc (2014) 45 (Suppl 1):S103–S107
DOI 10.1007/s12029-013-9577-4

CASE REPORT

Hepatocellular Carcinoma Presenting As Bile Duct Tumor: A Case Report

Luca Seriau · Cosimo Alex Leo · Rossano Girometti · Claudio Avellini · Umberto Baccarani · Alessandro Uzzau

Published online: 10 January 2014
© Springer Science+Business Media New York 2014

Case Report

G.G., a 78-year-old Caucasian male was presented to our attention complaining of continuous upper abdominal pain, jaundice, and melena. The patient referred to us that the symptoms started 3 days before.

His previous medical history comprised left superior lung lobectomy 11 years before for a non small-cell carcinoma (pT3N0M0), atypical hepatic resection for well-differentiated hepatocellular carcinoma (HCC) 7 years before, a prostatic adenocarcinoma (pT2aN0M0 GS 3-4) 3 years before, treated by radical prostatectomy with following radiotherapy, and sigmoid resection for colic adenocarcinoma (pT3N0M0 G2) 2 years later. In addition, he was in anticoagulant therapy for chronic atrial fibrillation and a pacemaker has been placed for an atrial-ventricular complete blockage.

Tumor markers showed normal values (alfa-phetoprotein, carcinoembryonic antigen (CEA), and carbohydrate antigen 19.9 (CA 19.9)) and hepatitis serology (HBV and HCV) was negative. Liver function tests were as follow, total bilirubin 2.90 mg/dL, unconjugated bilirubin 0.41 mg/dL, gamma-GT 1,335 UI/L, alkaline phosphatase 631 UI/L, glutamic oxaloacetic transaminase (GOT) 46 UI/L, glutamic-pyruvic transaminase (GPT) 55 UI/L. Blood cell counts showed Hb 12.5 g/dL, WBC 6.000, RBC 4.800.000, and platelet (PLT) 244.000.

A CT scan of the abdomen showed a main biliary duct dilated up to 11 mm with elongated morphology and lobulated profiles with presence of a solid tissue inside. It appeared as a lateral wall thickening with a diameter of 2.4×1.5 cm and extended longitudinally for 2.5 cm determining an apparent luminal stricture. This tissue had an early and intense contrast enhancement in the arterial phase with mild wash-out in the balance phase. CT of the thorax was negative.

On the base of CT, we decided to perform endoscopic retrograde cholangiopancreatogram (ERCP) and ultrasound endoscopy: ERCP showed a dilated biliary tract with a clot in the medial and distal third. The clot was removed after papillosphinterectomy. The underlying mucosa was macroscopically normal. Ultrasound endoscopy demonstrated a hypoecoic lesion at the middle third of the main bile duct. It had an ovular shape (length 23 mm, thickness 10 mm) and was vascularized at the power-doppler examination: the suspect of origin from the cystic duct's stump rose. The main bile duct was infiltrated and compressed and it had a slight increase in size up to the hepatic hilum. A minimal dilation of intrahepatic duct was also described. The distal portion of common bile duct had a regular gage with walls with binary morphology as sludge deposition and aerobilia. At the hepatic hilum, a 1-cm lymph node with pathologic morphology was identified.

On the basis of imaging and laboratory findings, the diagnosis of "upper biliary tract tumor" was done and an explorative laparotomy was planned. The liver had a cholestatic appearance. An intraoperative ultrasound exploration

L. Seriau (✉) · C. A. Leo · U. Baccarani · A. Uzzau
Department of General Surgery, University Hospital, Piazzale Santa Maria della Misericordia 15, 33100 Udine, Italy
e-mail: luc1983@libero.it

R. Girometti
Institute of Diagnostic Radiology, University Hospital, 33100 Udine, Italy

C. Avellini
Department of Pathology, University Hospital, 33100 Udine, Italy

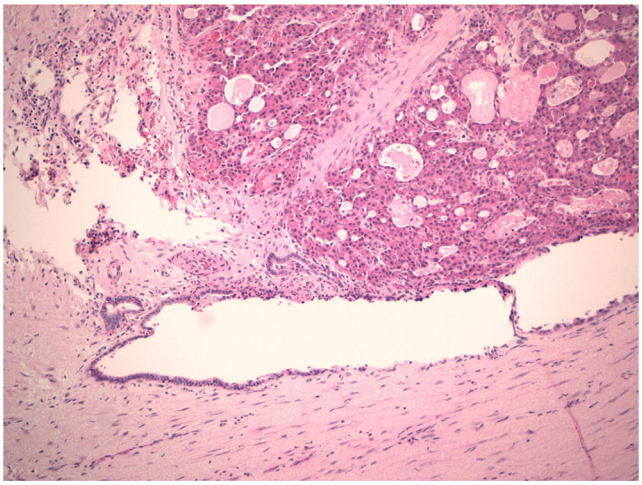


Fig. 1 Tubular-trabecular moderately differentiated hepatocellular carcinoma close to large biliary ductal structure. H&E, ×10

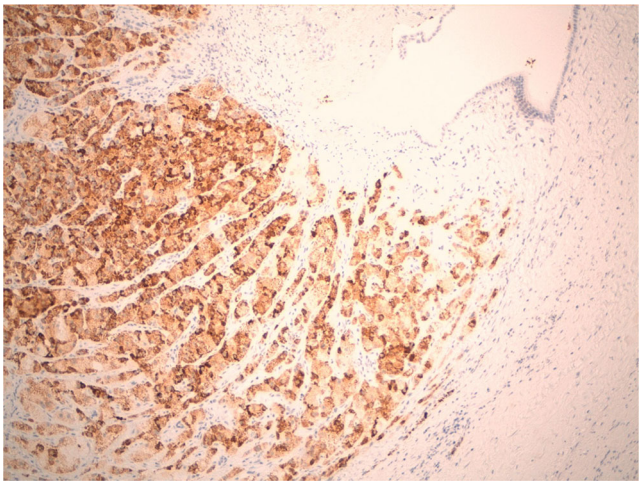


Fig. 3 Immunohistochemical reaction with anti-hepatocyte antibody: ductal neoplastic invasion. ×10

confirmed the presence of a homogeneous hypoechoic lesion located into the wall of the middle part of the common bile duct extended up to the hepatic duct bifurcation without signs of portal infiltration and inconsistent with the aspect of a typical cholangiocarcinoma of the main biliary duct. We performed a wedge biopsy of the lesion for cryostatic histological examination, which raised the diagnosis of hepatocellular carcinoma. A resection of the hepatic and common biliary duct and a bilio-jejunal anastomosis with Roux-en-Y reconstruction were then performed. Lymphadenectomy of the hepato-duodenal ligament was carried out.

Final histological examination confirmed the diagnosis of grade 2 hepatocellular carcinoma according to WHO. The tumor filled nearly all the resected biliary tract and had a hemorrhagic aspect with neoplastic vascular invasion. Immunohistochemical analysis showed hepar 1 positive in neoplastic cells, polyclonal CEA positive for canalicular reactivity, cytokeratin (CK) 7 negative, CK 20 negative, CK 19 negative, CA 19.9 negative, and CK 34beta E 12 negative (see Figs. 1, 2, 3, 4, and 5).

Tissues around the common biliary tract and the lymph nodes weren't involved in neoplastic spread and resected margins were free.

Nowadays, after 36 months, the patient is alive and well with no clinical, laboratoristic, or radiologic signs of tumor relapse. CEA, CA 19.9, and alfa-phetoprotein are within normal range values, GOT 41 UI/L, GPT 32 UI/L, alkaline phosphatase 120 UI/L, gamma-GT 60 UI/L, total bilirubin 1.7 mg/dL, unconjugated bilirubin 0.2 mg/dL, Hb 14.0 g/dL, WBC 5100, RBC 5.200.000, and PLT 260.000. CT and magnetic resonance cholangiopancreatography (MRCP) describe no dilatation of the biliary tract and no signs of hepatic and intraductal relapse.

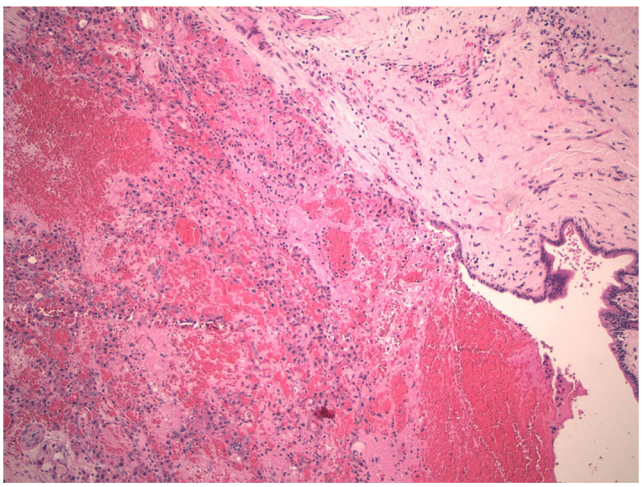


Fig. 2 Large ductal structure wall disrupted by neoplastic infiltration. H&E, ×10

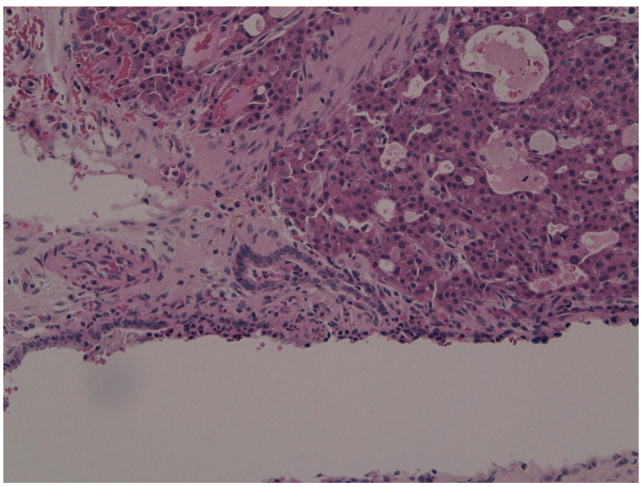
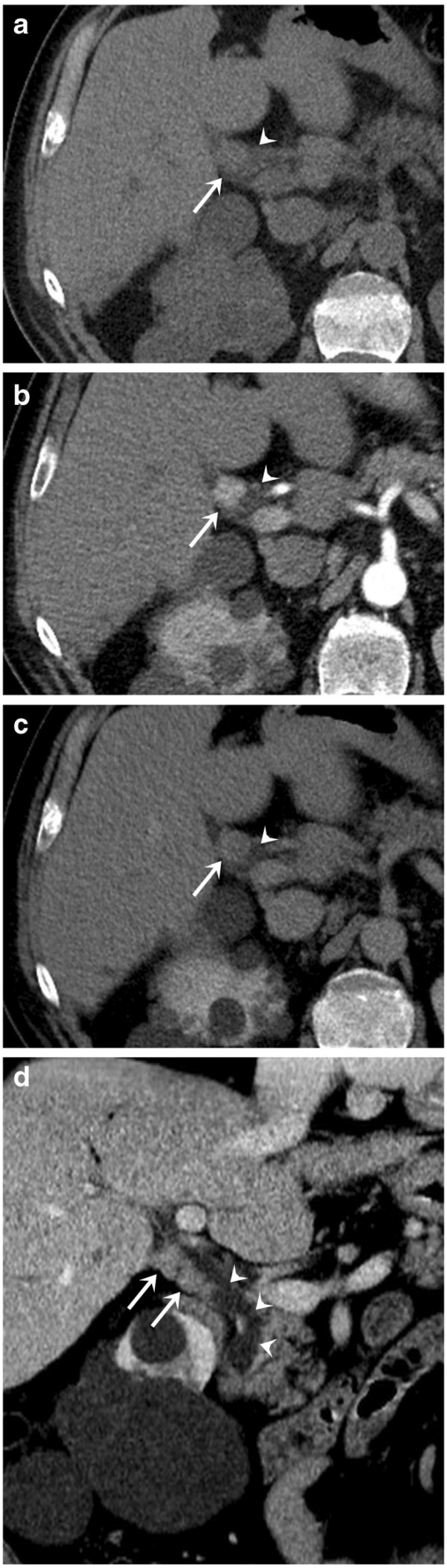


Fig. 4 Intraluminal neoplastic diffusion of HCC in large biliary ductal structure. H&E, ×20



◀ **Fig. 5** 64-raw computed-tomography axial images on direct (**a**), arterial (**b**), and equilibrium (**c**) phases showed a small round-shaped hypervascular mass (*arrows*) abutting the extrahepatic bile duct (*arrowheads*). Slight contrast medium wash-out was observed at the equilibrium phase (**c**). Coronally-reformatted image from the venous phase (**d**) better depicts the tight contact between the mass (*arrows*) and lateral wall of proximal extrahepatic bile duct (*arrowheads*). Biliary lumen was narrowed

Discussion

There are some classifications of HCC with bile duct thrombi (BDT) (Table 1 and 2) [1–3]. The presence of BDT was observed both in unifocal HCC and mostly in the multinodular type [4, 5]. The presence of BDT is associated more frequently with HCC with infiltrative or mixed pattern of growth, than with the expansive pattern. HCC associated to BDT are mainly poorly or mild differentiated HCC.

In patients affected by intrahepatic hepatocellularcarcinoma (IHCC) intrahepatic lesion is often smaller than in the "classic" HCC. In 2.9–25 % of patients with bile duct tumor thrombus (BDTT), intrahepatic lesion is not detectable [6].

Tumor thrombus usually appears as polypoid lesion with regular surface, hypervascularized. BDTT are strongly adherent to the biliary wall only in a small percentage of cases and they usually don't spread to the submucosal layer.

The main cause of BDTT is cholangiocarcinoma, followed by the diffuse type of HCC and gallstone obstructive disease of the biliary tree. Other rare conditions involving biliary obstruction are represented by liver metastasis of colonic adenocarcinoma origin, hepatic cystadenoma or cavernous hemangioma. The biliary tree can be a site of metastasis in particular of melanoma, less frequently by lung, breast, testis, prostatic, or pancreatic tumors [7, 8]. Primary sclerosing cholangitis, recurrent pyogenic cholangitis, acquired immunodeficiency syndrome cholangiopathy, autoimmune pancreatitis, inflammatory pseudo tumor, Mirizzi syndrome, xanthogranulomatomatous cholangitis, sarcoidosis, chemotherapy-induced sclerosis, lymphoma, leukemia, and carcinoid tumors are other rare forms of disease to be put sometimes in differential diagnosis.

Table 1 Incidence of IHCC

Author	Incidence of IHCC (%)	Number of cases
Huang et al. [17]	0.01	41
Huang et al. [18]	0.53	10
Qin et al. [14]	0.79	34
Esaki et al. [3]	3.4	40
Yeh et al. [19]	3.4	20

Table 2 Classification of HCC with BDT

Type	Ueda classification	Satoh classification	Esaki classification
I	Located in secondary branch	Limited to right or left hepatic duct with invasion of hepatic confluence	Macroscopic BDT Extended to CHD or principal or secondary intrahepatic ducts
II	Extended to first branch	Originated from right or left HD and extended to hepatic confluence	Microscopic BDT Limited to third order or also most peripheral parts of biliary tree
III	Extended to common hepatic duct (CHD) (IIIa); implanted tumor growing in CHD (IIIb)	BDT located far from the primitive tumor, in the CHD	
IV	Floating tumor debris from ruptured tumor in common bile duct		

IHCC pathogenesis can be summarized as follows:

- Origin from ectopic liver tissue in the biliary tract which undergo a cancerization process;

- Origin from a very small HCC that can't be identified at imaging studies;

Peng [9] described a new hypothesis for IHCC originating from liver stem/progenitor cells located in the Hering ducts that usually drain bile into the periportal space to little biliary ducts. In his hypothesis, the tumor first grows inside the intrahepatic biliary tract and only secondarily reaches the extrahepatic biliary tract.

Others [10, 11] described transcatheter arterial chemoembolization (TACE) for HCC as a rare risk factor for biliary tract involvement.

In our case, pathological examination of the specimen showed a well-circumscribed tumor and fully contained within the wall of the bile duct, without clear infiltration of the mucosal layer, so we hypothesized a trans-lymphatic dissemination of tumor cells during the previous hepatic resection, allowing the tumor cell to reach the submucosal layer of the upper biliary tract. However, biliary involvement realistically occurred in our patient 5 years before the onset of the symptoms. After 5 years, a new hepatic tumor is more common rather than a local relapse, especially considering the multiple previous neoplasms that affected the patient.

Table 3 1, 3, 5-years actuarial survival rates

Author	1 year (%)	3 years (%)	5 years (%)
Qin and Tang [10]	71.4	NA	NA
Peng et al. [12]	62.5	37.5	NA
Esaki et al. [3]	79	45	33
Lai and Lau [20]	57–100	20–47	7–45

If an IHCC is suspected, the diagnostic process includes abdomen CT and/or MRCP, ERCP with brushing and cleaning of the biliary tract, and a percutaneous transhepatic cholangiography in cases of severe obstructions. Nowadays MRCP is the best exam for a diagnosis of IHCC because it is not invasive.

The surgical approach is the standard therapy for IHCC; the aim is removing and cleaning the biliary tract from the thrombus with an associated hepatic resection. Some authors focus on drainage of the biliary obstruction before surgery as the better approach in those cases presenting with important jaundice. In this way, serum bilirubin can decrease before surgery in order to have a better resectability and to improve postoperative results [3, 5]. In those cases presenting with severe hemobilia, a selective hepatic arteriography is indicated with embolization of the artery feeding the neoplasm. The most common surgical approaches include right or left hepatic lobectomy (including removal of primitive tumor and tumor thrombus), hepatectomy with thrombus removal and choledochotomy with positioning of T-shaped bile drainage, internal bile drainage, or a biliary diversion. The gold standard treatment is the hepatic resection. Removing the biliary tract with BDT is indicated in those rare cases in which neoplastic infiltration of the biliary wall occurs. It can be avoided when the tumor thrombus is easily removable and in patients with impaired hepatic function. Liver transplantation for HCC with BDT has also been described [12, 13].

Absence of intrahepatic metastasis and a curative (R0) hepatic resection are considered positive prognostic factors of survival (Table 3). Some authors suggested local or systemic chemotherapy treatment after surgery [6, 14, 15] but more robust evidence are needed.

Cho et al. [16] reported that IHCC without intrahepatic lesion has a relative good prognosis with a simple local excision, in contrast with those forms associated with an intrahepatic primitive lesion. However IHCC's prognosis is always better than the classic HCC's prognosis.

Recurrences can localize only in the biliary tract or in the biliary tract together with an intrahepatic mass or exclusively with an intrahepatic lesion that is the most frequent condition.

More advanced cases can undergo a palliative approach in order to reduce biliary obstruction and jaundice. Percutaneous transhepatic biliary drainage or endoscopic biliary drainage with stent or prosthesis in the biliary tract can be performed. The intrahepatic lesion, if present and not resectable, can be treated with TACE or radiofrequency.

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

References

1. Lin TY, Chen KM, Chen YR, Lin WS, Wang TH, Sung JL. Icteric type hepatoma. Med Chir Dig. 1975;4:267–70.
2. Satoh S, Ikai I, Honda G, Okabe H, Takeyama O, Yamamoto Y, et al. Clinicopathologic evaluation of hepatocellular carcinoma with bile duct thrombi. Surgery. 2000;128:779–83. doi:10.1067/msy.2000.108659.
3. Esaki M, Shimada K, Sano T, Sakamoto Y, Kosuge T, Ojima H. Surgical results for hepatocellular carcinoma with bile duct invasion: a clinicopathologic comparison between macroscopic and microscopic tumor thrombus. J Surg Oncol. 2005;90(4):226–32. doi:10.1002/jso.20260.
4. Ikeda Y, Matsumata T, Adachi E, Hayashi H, Takenaka K, Sugimachi K. Hepatocellular carcinoma of the intrabilliary growth type. Int Surg. 1997;82(1):76–8.
5. Shiomi M, Kamiya J, Nagino M, Uesaka K, Sano T, Hayakawa N, et al. Hepatocellular carcinoma with biliary tumor thrombi: aggressive operative approach after appropriate preoperative management. Surgery. 2001;129(6):692–8. doi:10.1067/msy.2001.113889.
6. De Raffele E, Mirarchi M, Bassi F, Cola B. Carcinoma epatocellulare con trombosi neoplastica del dotto epatico comune. Chir Ital. 2008;60(6):849–62. article in Italian.
7. Menias CO, Surabhi VR, Prasad SR, Wang HL, Narra VR, Chintapalli KN. Mimics of cholangiocarcinoma: spectrum of disease. Radiographics. 2008;28(4):1115–29. doi:10.1148/rg.284075148.
8. Buckmaster MJ, Schwartz RW, Carnahan GE, Strodel WE. Hepatocellular carcinoma embolus to the common hepatic duct with no detectable primary hepatic tumor. Am Surg. 1994;60(9):699–702.
9. Peng N, Li L, Cai X, Tan S, Wu T. Liver stem/progenitor cells in the canals of hering: cellular origin of hepatocellular carcinoma with bile duct tumor thrombi? Stem Cell Rev. 2010;6(4):579–84. doi:10.1007/s12015-010-9188-4.
10. Qin LX, Tang ZY. Hepatocellular carcinoma with obstructive jaundice: diagnosis, treatment and prognosis. World J Gastroenterol. 2003;9(3):385–91.
11. Spahr L, Frossard JL, Felley C, Brundler MA, Majno PE, Hadengue A. Biliary migration of hepatocellular carcinoma fragment after transcatheter arterial chemoembolization therapy. Eur J Gastroenterol Hepatol. 2000;12:243–3. doi:10.1097/00042737-200012020-00018.
12. Peng SY, Wang JW, Liu YB, Cai XJ, Deng GL, Xu B, et al. Surgical intervention for obstructive jaundice due to biliary tumor thrombus in hepatocellular carcinoma. World J Surg. 2004;28(1):43–6.
13. Lee KW, Park JW, Park JB, Kim SJ, Choi SH, HEo JS, et al. Liver transplantation for hepatocellular carcinoma with bile duct thrombi. Transplant Proc. 2006;38(7):2093–4. doi:10.1016/j.transproceed.2006.06.034.
14. Qin LX, Ma ZC, Wu ZQ, Fan J, Zhou XD, Sun HC, et al. Diagnosis and surgical treatments of hepatocellular carcinoma with tumor thrombosis in bile duct: experience of 34 patients. World J Gastroenteol. 2004;10(10):1397–401.
15. Fukuda S, Okuda K, Imamura M, Imamura I, Eriguchi N, Aoyagi S. Surgical resection combined with chemotherapy for advanced hepatocellular carcinoma with tumor thrombus: report of 19 cases. Surgery. 2002;131(3):300–10. doi:10.1067/msy.2002.120668.
16. Cho HG, Chung JP, Lee KS, Chon CY, Kang JK, Park IS, et al. Extrahepatic bile duct hepatocellular carcinoma without primary hepatic parenchymal lesions. A case report. Korean J Intern Med. 1996;11(2):169–74.
17. Huang GT, Sheu JC, Lee HS, Lai MY, Wamg TH, Chen DS. Icteric type hepatocellular carcinoma: revisited 20 years later. J Gastroenterol. 1998;33(1):53–6. doi:10.1007/PL00009966.
18. Huang JF, Wang LY, Lin ZY, Chen SC, Hsieh MY, Chuang WL, et al. Incidence and clinical outcome of icteric type hepatocellular carcinoma. J Gastroenterol Hepatol. 2002;17(2):190–5. doi:10.1046/j.1440-1746.2002.02677.
19. Yeh CN, Jan YY, Lee WC, Chen MF. Hepatic resection for hepatocellular carcinoma with obstructive jaundice due to biliary tumor thrombi. World J Surg. 2004;28(5):471–4. doi:10.1097/00000658-199703000-00007.
20. Lai EC, Lau WY. Hepatocellular carcinoma presenting with obstructive jaundice. ANZ J Surg. 2006;76(7):631–6. doi:10.1111/j.1445-2197.2006.03794.