

# Non-Cirrhotic Hepatocellular Carcinoma with Duodenal Metastasis in Chronic Hepatitis B: Case Report

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## ABSTRACT

**Background:** Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The extrahepatic extension is also more common in non-cirrhotic HCC. It most commonly metastasizes to the regional lymph nodes, bone, and lungs. Metastasis to the small bowel is rare. Further, hematogenous metastasis to the duodenum is incredibly rare. **Case:** A 67-year-old man was admitted with a recurrence of hematemesis melena, weight loss, weakness, and decreased appetite. There was a history of hepatitis and a family history of liver diseases. Abdominal examination revealed a palpable liver (8 cm below the right costal margin, firm, irregular, and tender). Laboratory studies revealed Hb 5.2 g/dL, SGOT 301.1 u/L, SGPT 244.7 u/L, albumin 2.7 g/dL, HbsAg was reactive with HBV DNA 2.01 x 10<sup>4</sup> IU/ml. EGD showed that esophageal varices were not visible, the duodenum showed an irregular mass, bleeding on touch, and many blood clots. Abdominal USG revealed hepatomegaly with suspicion of multifocal hepatoma, while a CT scan suggested the appearance of HCC and no local invasion into the small bowel. The result of the fibro scan was severe fibrosis, not cirrhosis. At laparotomy, a hepatic tumor and duodenum were discovered. The histopathological study of the tumor revealed a well-differentiated HCC. The resection of the tumor could not be done. He was given palliative and symptom treatment HCC on non-cirrhotic liver remains an exceptional condition. **Conclusion:** We report a non-cirrhotic HCC in chronic hepatitis B infection.

**Keywords:** hepatocellular carcinoma; non-cirrhotic; hepatitis; hematemesis; hepatomegaly

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the second leading cause of cancer-related death. The prognosis for HCC is poor in all regions of the world. Thus, the average incidence and death rates are almost the same. In 2018, the estimated incidence of liver cancer per 100,000 people in one year was 9.3, while the mortality rate was 8.5. The most common risk factor for developing HCC is a chronic hepatitis B virus (HBV) infection. In 80-90% of cases, HCC develops on a cirrhotic background, but non-cirrhotic HCC occurs in 15-20% of cases. HCC in a non-cirrhotic liver without any of the risk factors is rare. Around 30% of HBV-related HCC occurs in non-cirrhotic patients. (1,2)

HCC common metastases through blood vessels or lymphatics to the local lymph nodes, lungs, and bone. Metastasis to the small bowel is uncommon, and a few cases of small bowel involvement have been reported only as case reports or case series. In most reported cases, small intestine involvement was located on the proximal duodenum because of direct extension from the primary tumor. Furthermore, Hematogenous or lymphatic metastasis to the duodenum is extraordinarily rare. (3,4) The present case report describes a 67-year-old man patient admitted to the hospital with recurrent hematemesis melena; he was diagnosed with HCC with duodenal metastasis in chronic HBV infection.

## CASE REPORT

A 67-year-old male was admitted with the main complaint of hematemesis melena two months ago. Other complaints were upper right abdominal pain, weight loss, weakness, and decreased appetite. The patient had a history of hepatitis B. There were no reports of comorbidities like diabetes, obesity, other infections, or alcohol abuse. The patient's family had a history of unspecific liver disease. He was abstinent from alcohol and was not a tobacco smoker; he denied any intravenous drug abuse, blood transfusions, sexual promiscuity, or history of hepatitis.

On physical examination, he appeared sick and had anemia. He was not icteric or pale, and there was no bilateral leg edema or peripheral stigmata of chronic liver cell disease or signs of hepatic failure. His cardiovascular system examination was regular, with normal blood pressure. An abdominal study revealed a palpable liver (8 cm below the right costal margin, irregular, firm, and tender), no splenomegaly or ascites. Examination of other systems was unremarkable. Initial laboratory studies, cell blood count (CBC) revealed WBC 6.16 x 10<sup>3</sup> u/L, Hb 5.2 g/dL, MCV 84.7 fL, MCHC 22.00 fL, Platelet 515 x 10<sup>3</sup> u/L. Renal test showed ureum 70.5 mg/dL, creatinine 0.28 mg/dL. Liver test revealed SGOT 301.1 u/L, SGPT 244.7 u/L, total bilirubin 3.68 mg/dL, direct bilirubin 0.73 mg/dL, indirect bilirubin 2.95 mg/dL, albumin 2.7 g/dL, globulin total 3.0 g/dL, and protein total 5.79 g/dL. Serologies for HBV, such as HbsAg, were reactive with HBV DNA 2.01 x 10<sup>4</sup> IU/ml, while anti-HCV was non-reactive.

Esophagogastroduodenoscopy (EGD) showed that esophageal varices were not visible, gastric was expected, and the duodenum showed an irregular, brittle mass bleeds easily, blood clots, and the scope could not enter. Ultrasonography (USG) of the abdomen revealed hepatomegaly with two solid groups in the right lobe suspicious of multifocal hepatoma. While the computerized abdomen tomography (CT) scan found a heterogeneous solid mass with a necrotic component in segment IVA/B, an enlarged liver V exotically inferiorly with suspicion of proper posterior abdominal wall infiltration, deviating abdominal aorta, portal vein, IVC, and head of the pancreas towards the left lateral, and pushes the right kidney posteriorly, suggesting the appearance of HCC. The result of the fibroscan was 10.7 kPA, Metavir grade 3. It was severe fibrosis, not cirrhosis. At laparotomy, discovered an irregular firm tumor hepatic and duodenum. Unfortunately, the resection of the tumor in the liver and duodenum could not be done; the patient underwent gastrojejunostomy and jejunostomy. The histopathological study of the surgical biopsy of the tumor revealed a well-differentiated HCC. No eosinophilic, polygonal cells or wide lamellar bands of fibrous tissue are characteristic of the fibrolamellar HCC.

The patient was diagnosed with HCC BCLC stage C with duodenal metastasis in chronic HBV infection. He was given palliative and symptoms treatment, such as RL: D5: amino fusion, transfuse PRC for anemia, transfuse albumin for hypoalbumin, tenofovir 300 mg, spironolactone 100 mg, morphine slow-release tablet (MST), and Curcuma. After the patient's condition improved, the patient was allowed to head home. The patient was recommended to visit a more sophisticated hospital.

## DISCUSSION

There are limited studies on the pathogenesis and management of HCC in non-cirrhotic liver. Risk factors for developing HCC have been identified, including cirrhosis of almost any cause, chronic hepatitis B virus (HBV) or hepatitis C virus (HCV), alcohol, non-alcoholic steatohepatitis, and hemochromatosis. HCC development in the non-cirrhotic liver was less than 20%. Compared to HCC in a cirrhotic liver, HCC without cirrhotic liver has some peculiarities. Many studies have shown that most patients with non-cirrhotic HCC are male and bimodal age distribution, peaking in the second and seventh decades. (1,5,6) In the presented case, a patient was a man aged about sixty.

One of the most common causes of non-cirrhotic HCC is a chronic HBV infection, especially in high-incidence areas. Up to 30% of HBV-related HCC arise in non-cirrhotic livers. (7) HBV is a partially double-stranded DNA virus that can integrate into the host cell and acts as a mutagenic agent causing secondary chromosomal rearrangement and increasing genomic instability or producing genotoxins such as the HBx protein, resulting in HCC development in non-cirrhotic backgrounds. (1,7,8) Transactivation of genes by the regulatory protein HBx interferes with tumor-suppressor activity through its interaction with p53. It increases cell proliferation, deregulates cell cycle control, and interferes with DNA repair and apoptosis. High viral load titers (10<sup>4</sup>-5 copies/mL) have been linked with PIK3CA mutations and be an independent risk factor for non-cirrhotic HCC. (7,8) Certain risk factors in chronic hepatitis B patients, in turn, impart a higher risk for non-cirrhotic HCC. BCP T1762/A1764 mutation and high viral loads have been substantial viral factors and independent predictors of HCC in non-cirrhotic patients who are chronic HBV carriers. Older patients with chronic Hepatitis B had a higher incidence of non-cirrhotic HCC than cirrhotic patients; 1.1% per year in men and 0.3%-0.4% per year in women older than 55 years old. (1)

HCC is very aggressive and often detected in late and inoperable stages due to early stages; it is clinically silent because of a lack of symptoms, surveillance imaging, and higher hepatic reserve in this population. More than 60% of patients are diagnosed after extrahepatic metastasis has occurred. (1,6) The most common presenting symptom is abdominal pain (52%). Other symptoms are abdominal distention, weight loss, malaise, anorexia, fatigue, chronic diarrhea, jaundice, chest pain, and fever of unknown origin. It can also present in the form of the paraneoplastic syndrome of hypercalcemia or hypoglycemia. (1,9,10) As in our patient, the tumor was diagnosed at an advanced stage, and the main complaint was hematemesis melena recurrent due to extrahepatic metastasis at the duodenum. Other symptoms, such as upper right abdominal pain, weight loss, weakness, and decreased appetite, are not specific. The hepatic parenchyma surrounding non-cirrhotic HCC can be entirely normal but usually shows some degree of fibrosis (41-65%), inflammation (50%), early steatosis (36%), or iron accumulation. (3,8,11) In our patient, the fibroscan revealed Metavir F3. It was severe fibrosis.

The radiological appearance of HCC in non-cirrhotic and cirrhotic patients is very similar, except HCC in non-cirrhotic livers frequently presents as a solitary mass with or without satellite lesions, much larger in tumor size, and is often seen with a central scar. Rarely can there be multiple masses without a dominant lesion. The right lobe appears to be commonly involved in non-cirrhotic HCC, whereas fibrolamellar HCC is more common in the left lobe. (1,8,12) USG allows determining the lesion's size, location, morphology, and vascular involvement. The appearance is variable and non-specific, ranging from hypo or hyperechoic lesions with or without heterogeneity or necrotic areas. (1,3,9) In this case, the USG abdomen revealed hepatomegaly with two solid masses in the right lobe, suspicious of multifocal hepatoma. The abdominal CT scan can diagnose HCC with a high degree of confidence. Hence proper technique and contrast administration are crucial for an accurate assessment. It often revealed a single large, well-circumscribed encapsulated hypoattenuating lesion on unenhanced CT, with foci of hemorrhage, necrotic areas, and fat involvement more common in non-cirrhotic HCC. MRI is superior to CT scan for diagnosing HCC appearance on T1 sequences, depending on fibrosis, necrosis, and fat. However, it more commonly presents as a hypointense lesion. (1,8,9) The abdominal CT scan performed in the presented case suggested hepatocellular carcinoma. It presents as a heterogeneous solid mass with a necrotic component in it in segment IVA/B, an enlarged liver V exotically inferiorly with suspicion of right posterior abdominal wall infiltration, deviating abdominal aorta, portal vein, IVC, and head of the pancreas towards the left lateral, and pushes the right kidney posteriorly.

Histological diagnosis through liver biopsy may also be necessary if imaging studies are inconclusive for being well-matched with HCC. The AASLD no longer proposes biopsy for lesions > 1 cm if specific imaging studies yield concordant findings. They may be completed through the transabdominal method underneath CT or US guidance with various sensitivity levels (66%-93% based on tumor size) and 100% specificity and positive predictive value. Liver biopsy can be needed in patients who are not candidates for resection to establish a diagnosis for systemic therapy or transplantation. In step with histological classification criteria of the world health organization (WHO), the trabecular type is the most frequent form (41-76%) in non-cirrhotic HCC, as it is far in cirrhotic subjects. (1,8)

The extrahepatic extension is more common in HCC without cirrhosis liver. HCC in non-cirrhotic patients was more advanced (stage III or IV) (52.3% vs 45.5%,  $p=0.002$ ) and more frequently presented as single (37.0% vs 34.4%,  $p<0.001$ ) or large multinodular lesions (24.7% vs 21.5%,  $p<0.001$ ) with vascular invasion or extrahepatic spread (36.3% vs 33.5%,  $p<0.001$ ). (2) Hematogenous metastasis to the duodenum from any primary malignancy is generally uncommon, including HCC to the duodenum. Several primary tumors have reported hematogenous metastasis to the duodenum, such as lung carcinomas and breast and malignant melanoma. Isolated duodenal metastasis from HCC is rare, as described in this case. This uncommon presentation posed each a diagnostic and management challenge. (3,4,13) In this patient with regarded multifocal HCC, duodenal lesions equivalent to liver parenchyma have been discovered endoscopically and laparotomy, elevating the suspicion that those lesions have been metastasis deposits of HCC. Most duodenal involvement with HCC results from local extension of the primary tumor, but the CT scan and laparotomy proved no local invasion into the small bowel. In addition, no distant metastasis disease was noted on CT scan staging, especially in common sites of distant metastasis such as lungs and bones.

Treatments for HCC include oral or intravenous chemotherapy, surgery, liver transplantation, transarterial chemoembolization (TACE), radiofrequency ablation (RFA), alcohol ablation, preoperative portal vein embolization, and sorafenib therapy. In the absence of prominent fibrosis, the main treatment methods for HCC are hepatectomy, liver transplantation, and local ablation. Surgical resection is the treatment of preference for non-cirrhotic HCC. Indications for surgery are tumors without liver cirrhosis or portal hypertension. Second and third hepatectomy for recurrent non-cirrhotic HCC appears safe and effective compared to primary resection. The 5-year total survival after surgical resection of non-cirrhotic HCC is much higher (44-58% of patients) than resection of HCC in cirrhosis (23-48% of patients). (1,11,12) Sorafenib is a US Food and Drug Administration-approved oral multikinase inhibitor that antagonizes tumor cell proliferation and neoangiogenesis. Sorafenib may be helpful in the treatment of unresectable tumors. However, its effect on long-term outcomes as an adjunct to surgical resection of non-cirrhotic HCC remains undetermined. Numerous chemotherapy regimens have additionally been evaluated in the palliative setting, without a specific single agent or mixture chemotherapy regimen found to be especially effective or superior. (1,11,12) In this case, unfortunately, the resection of the tumor in the liver and duodenum could not be done; the patient underwent gastrojejunostomy and jejunojunostomy to allow food and other stomach contents to pass directly from the stomach to the jejunum without passing through the duodenum. He was given palliative and symptoms treatment, such as RL: D5: amino fusion, transfuse PRC for anemia, transfuse albumin 25% for hypoalbumin, tenofovir 300mg, spironolactone 100 mg, MST, and Curcuma.

The prognosis for HCC is poor in all regions of the world. Survival of patients with HCC in the non-cirrhotic liver mainly depends on tumor-related factors such as tumor size, satellite lesions, lack of tumor capsule, vascular invasion, grading, incomplete resection, HBV infection, and the number of intraoperative blood transfusions. (1) The mortality rate of patients with non-cirrhotic HCC is similar to that of patients with cirrhotic HCC, even though cirrhotic HCC can be found early. In contrast, non-cirrhotic HCC is usually found at a late stage. Late diagnosis is an important reason for the poor prognosis of patients with non-cirrhotic HCC.

However, non-cirrhotic HCC is more amenable to hepatic resection due to the lower risk of liver failure. Patients without cirrhosis have more remarkable extended survival (overall postoperative and recurrence-free) than patients with cirrhosis. Nevertheless, the recurrence rate of HCC in non-cirrhotic livers could be excessive after surgical resection. (9,14)

## CONCLUSION

Non-cirrhotic HCC is a complex disease with different risk factors, pathogenesis, clinical manifestations, management, and prognosis from cirrhotic counterparts. We report an HCC with chronic hepatitis B without liver cirrhosis. The pathogenesis is still not well understood. It is characterized by delayed diagnosis and, consequently, a poor prognosis at an advanced stage. The suspicion of duodenal metastasis via hematogenous also makes this case unique. Early and definitive diagnosis of HCC is essential to prevent such devastating complications as tumor rupture with subsequent hemorrhagic shock and death.

## COMPETING INTERESTS

No competing interests were disclosed.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

## ETHICAL APPROVAL

The patient has given permission and informed consent to publish this case report.

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