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Case Report

Synchronous hepatocellular carcinoma with renal cell carcinoma: a case report and review of literature

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Abstract: The discovery of synchronous double malignancies in the same patient is not uncommon. Whereas co-existence of hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) is extremely rare, and the number of reported cases is very limited in the English-language literature to date. We present a case of a 53-year-old man who was found to have HCC and RCC during an incidental medical examination. The patient underwent left hemihepatectomy and right radical nephrectomy, and histological and immunohistochemical examination confirmed that the tumor originating from the left lateral hepatic lobe was HCC, and the tumor arising from the lower portion of the right kidney was clear cell RCC. A follow-up period of 18 months was uneventful. The pathogenesis and previous related reports of these lesions are discussed.

Keywords: Synchronous double primary malignancies, hepatocellular carcinoma, renal cell carcinoma, hemihepatectomy, nephrectomy

Introduction

Synchronous cancers are exceptional, accounting for 3.7% of all cancers, with no significant age difference between patients with single cancers and multiple malignancies [1]. Multiple primary malignant neoplasms are rare in the hepatocellular carcinoma patients, and the most common site of extrahepatic primary malignancy (EHPM) was the gastrointestinal system with adenocarcinoma of the colon or gastric carcinoma as most common tumor [2]. Whereas the frequency of multiple synchronous hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC) is extremely rarer, and to the best of our knowledge, only 5 cases reports could be found in the international literature to date. Herein, we report a case of synchronous HCC and RCC, including clinical and histopathological features, clinical prognosis, and diagnostic and therapeutic approaches, following a comprehensive literature review.

Case report

A 53-year-old male was admitted to the Department of Hepatobiliary Surgery of the Harrison International Peace Hospital (Hengshui, China) with space-occupying lesions in the liver and right kidney during an incidental abdominal ultrasound while undergoing a medical examination for health checkup. The patient had no right upper quadrant abdominal pain and flank pain, urologic symptoms and nor history of gross hematuria. The patient had a previous history of diabetes mellitus for 6 years. He has no family history of cancer. On admission, the vital signs were all within the normal ranges (body temperature, 36.3°C; heart rate, 80 beats/min; respiration rate, 20 times/min; blood pressure, 121/88 mmHg). On physical examination, the abdomen was soft, but tender in the right upper quadrant. Routine laboratory examination were all ranked in normal limits, including routine blood chemistry, complete blood count, liver and kidney function tests, and urine analysis, but the result of alphafetoprotein (AFP) was 1000 ng/ml. The HBsAg, Anti-HBs and Anti-HCV were all negative. Enhanced computerized tomography (CT) examination of the abdomen revealed a round-like, heterogeneous enhancement, solid and well-circumscribed tumor originating from the left lateral hepatic lobe, measuring 11.0 cm×9.4 cm (**Figure 1A**). The CT scan also revealed a 4.3 cm×3.8 cm and mildly-enhanced, mixed-density and exog-

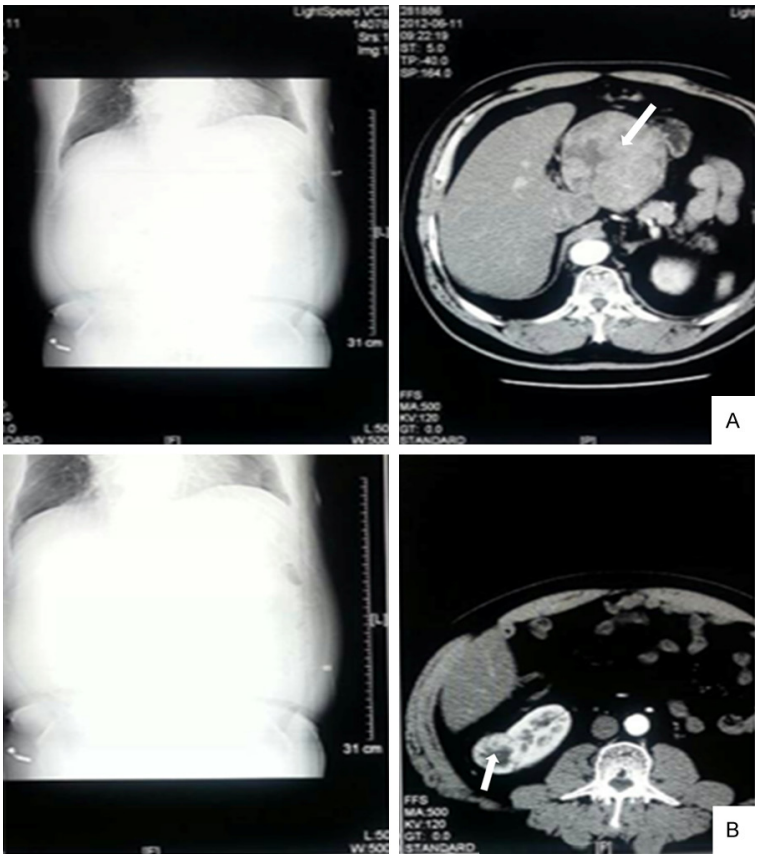

Figure 1. Computed tomographic (CT) images showed a round-like, heterogeneous enhancement, solid and well-circumscribed tumor (white arrow) originating from the left lateral hepatic lobe, measuring 11.0 cm×9.4 cm (A), and a 4.3 cm×3.8 cm and mildly-enhanced, mixed-density and exogenous mass (white arrow) in the lower portion of the right kidney (B).

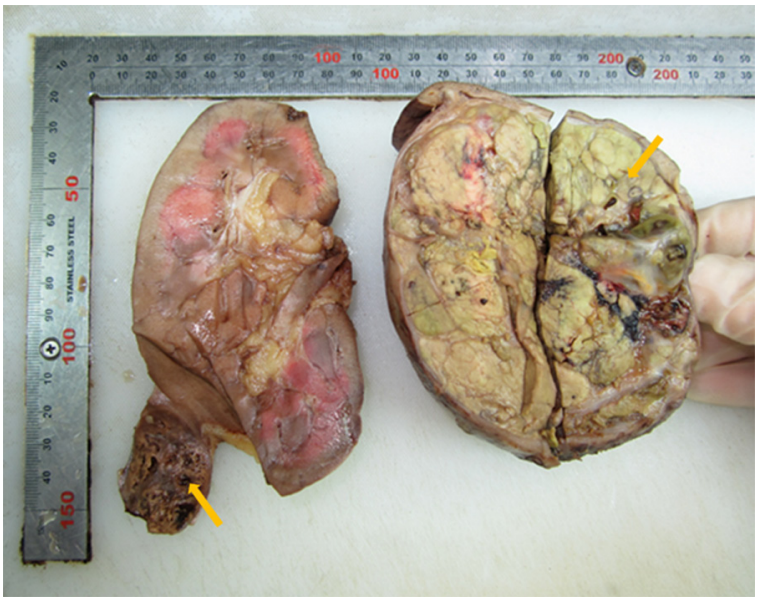

Figure 2. Gross appearance of the resected specimen (12.0 cm×7.0 cm×4.0 cm) of the renal neoplasm was smooth surface, bisected to reveal a 4.5 cm×3.5 cm×2.0 cm circumscribed and solid tumor (yellow arrow) in grayish yellow and red color (Left), and the resected speimen (14.0 cm×9.0 cm×8.0 cm) of the hepatic neoplasm was slight granular surface, bisected to reveal a 10.0 cm×8.0 cm×8.0 cm boundary clear but unencapsulated firm tumor (yellow arrow) in grayish white and yellow color, and local hemorrhage was seen (Right).

enous mass in the lower portion of the right kidney but no sign of local invasion or lymph node metastases (**Figure 1B**). The imaging investigation was indicative of HCC and RCC, and resection of the left hemihepatectomy and right radical nephrectomy was performed. The post-operative course was uneventful, and adjuvant chemoradiation therapy was given, as the HCC tumor was particularly large (diameter, >10.0 cm). A follow-up period of 18 months with clinical and abdominal CT examination, liver function tests and tumor marker (AFP) has been monitored. The patient was still alive and well without clinical and radiological evidence of local recurrence and distant metastasis.

Pathologic findings

On gross examination, the resected specimen (14.0 cm×9.0 cm×8.0 cm) of the hepatic neoplasm was slight granular surface, bisected to reveal a 10.0 cm×8.0 cm×8.0 cm boundary clear but unencapsulated firm tumor in grayish white and yellow color, and local hemorrhage was seen (**Figure 2**). Another resected specimen (12.0 cm×7.0 cm×4.0 cm) of the renal neoplasm was smooth surface, bisected to reveal a 4.5 cm×3.5 cm×2.0 cm circumscribed and solid tumor in grayish yellow and red color (**Figure 2**). Microscopically, the neoplastic cells of the hepatic neoplasm arranged in sheet, which

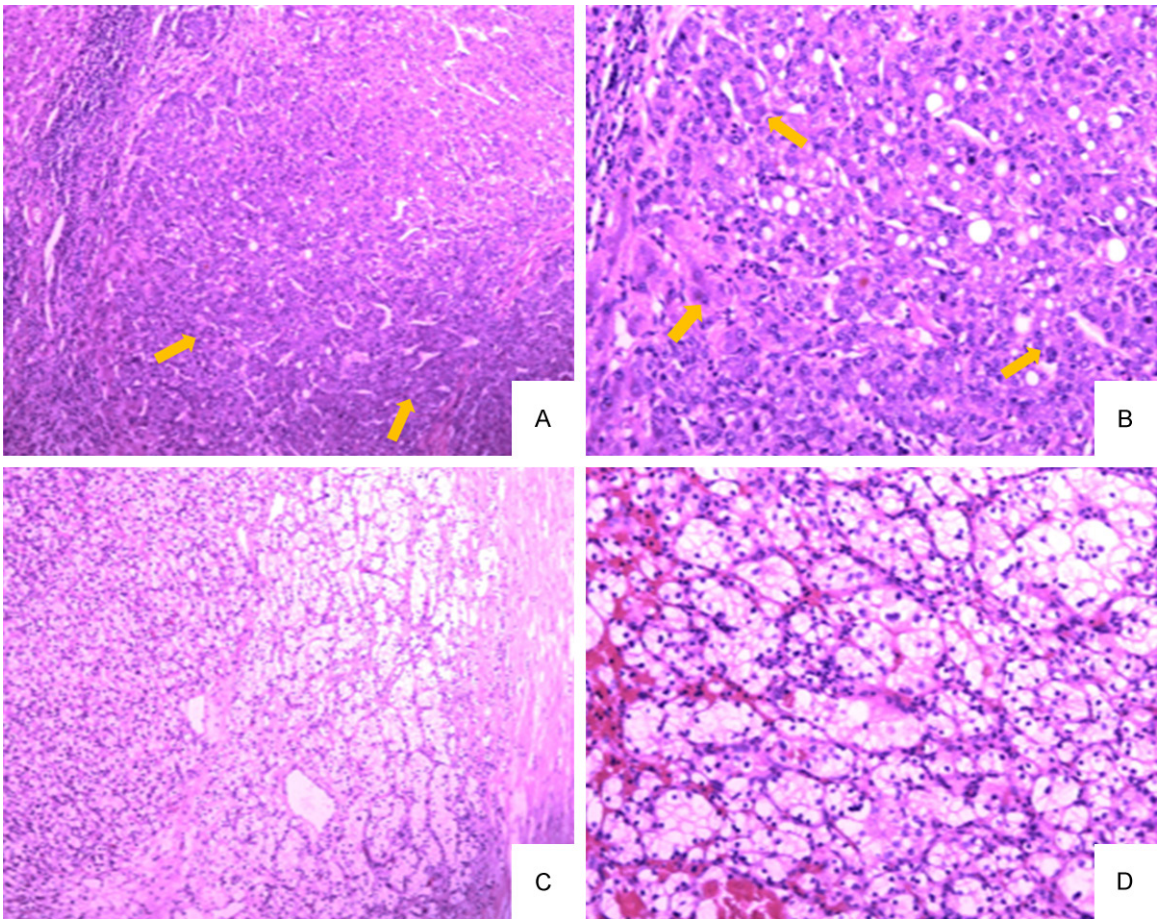

Figure 3. Microscopic features of HCC and RCC. (A) The neoplastic cells of the hepatic neoplasm arranged in sheet, which were separated by a sinusoid blood vessel (Hematoxylin-eosin [H&E], 40×); (B) The neoplastic cells were round or polygonal shape, which were characterized with large, basophilic, heteromorphic nucleoli, and their cytoplasm was eosinophilic (HE, 200×, yellow arrow). (C) The tumor cells of the kidney neoplasm arranged in acinar, cystic and solid sheet (HE, 40×), which were medium size with transparent cytoplasm, spherical and irregular nucleus (yellow arrow), but nucleoli were not obvious (D: HE, 200×).

were separated by a sinusoid blood vessel (**Figure 3A**). The neoplastic cells were round or polygonal shape, which were characterized with large, basophilic, heteromorphic nucleoli, and their cytoplasm was eosinophilic (**Figure 3B**). In addition, the dividing line of the malignant cells was not clear. The tumor cells of the kidney neoplasm arranged in acinar, cystic and solid sheet (**Figure 3C**), which were medium size with transparent cytoplasm, spherical and irregular nucleus, but nucleoli were not obvious (**Figure 3D**). Immunohistochemically, the hepatic neoplastic cells were positive reaction for HepPar-1 (**Figure 4A**) and GPC3 (**Figure 4B**), and negative for CD10 and Pax-8. However, the renal neoplastic cells were positive reaction for Pax-8 (**Figure 4C**) and CD10 (**Figure 4D**), but negative for HepPar-1 and GPC3. The final histological diagnosis was simultaneous double primary carcinomas of the liver and kidney (Hepatocellular carcinoma in left lateral lobe of liver and clear cell renal cell carcinoma in right kidney).

Discussion

Multiple primary malignant neoplasms are referred to the same patient simultaneously or successively suffering from two or more primary malignancies of different histological types, which can affect multiple tissues and organs [3]. The diagnostic criteria for the accurate diagnosis of multiple primary malignancies includes: ① each tumor must present a histologically marked features of malignancy; ② each tumor should exhibit different morphologi-

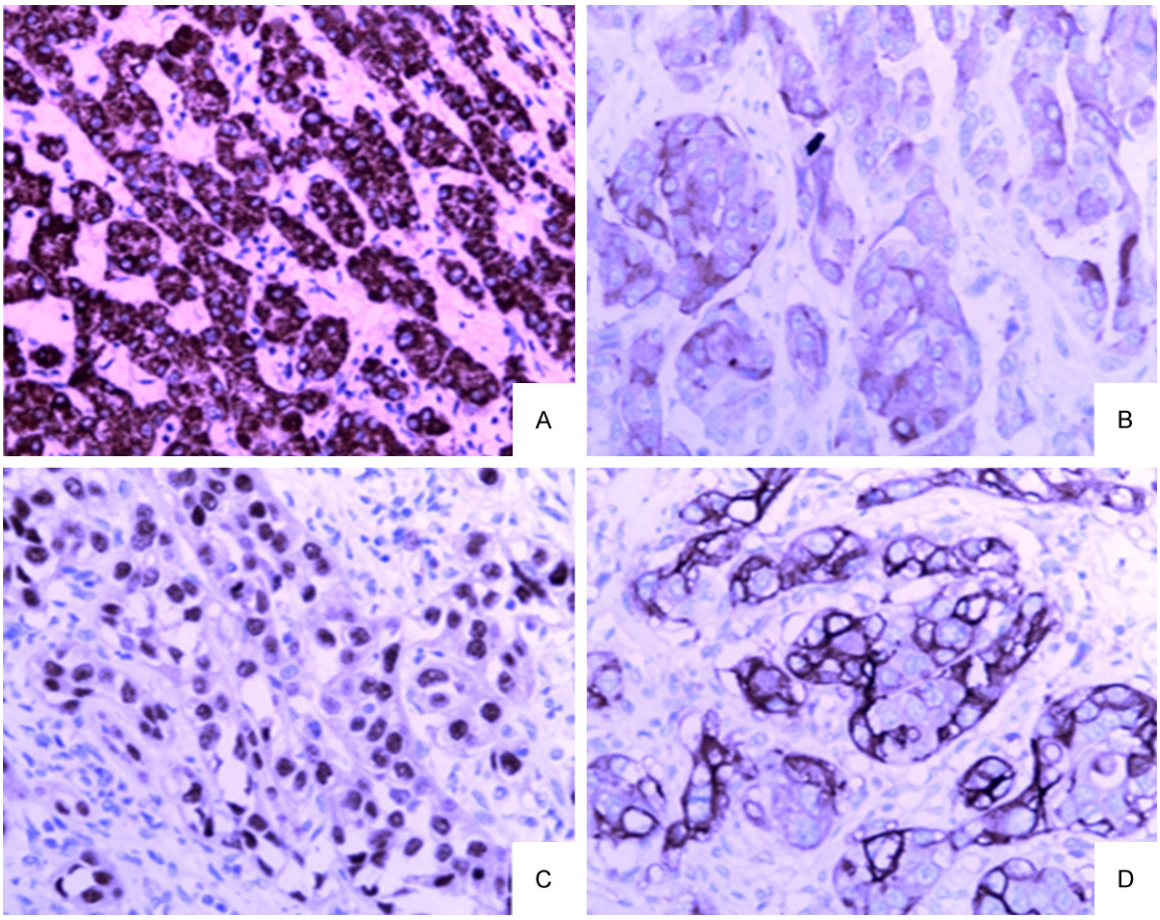

Figure 4. Immunohistochemically, neoplastic cells of the hepatic neoplasm were positive for HepPar-1 (A: EnVision ×200) and GPC3 (B: EnVision ×400). The tumor cells of the kidney neoplasm were positive for Pax-8 (C: EnVision ×200) and CD10 (D: EnVision ×400).

cal, histological and cytological features as well as immunohistochemical phenotype; ③ each tumor occurs in different parts or organs; ④ the possibility that one is a metastasis of another must be excluded clinically, radiologically and pathologically.

The incidence of HCC with extrahepatic primary malignancy (EHPM) ranged from 2.1 to 14.5% in some studies and the most common site of EHPM was the gastrointestinal system with adenocarcinoma of the colon or gastric carcinoma as most common tumor [2]. However, coexistence of hepatocellular carcinoma and renal cell carcinoma is extremely rare, and only 5 cases reported in the English literature [4-8]. The previously reported cases are summarized in **Table 1**, together with the current case. Nzeako et al. [2] researched results revealed the occurrence of HCC with EHPM is common at significantly older ages, and a predilection for men with a male-to-female of 11:1. The age of our patients range from 42 to 72 years (average, 56.7 years), and the patients were all men.

With an increase in the number of elderly patients and improvements in diagnostic techniques, multiple synchronous cancers have become more common. Although the mechanisms underlying the occurrence of multiple primary malignancies have not been clarified, certain factors have been implicated, including heredity, carcinogenic virus, environmental and immunological factors, and radiological and chemical treatments [9]. Nzeako et al. [2] researched results showed patients having HCC with cirrhosis were 1.8 times more likely to have an EHPM than noncirrhotic HCC patients. Reviewing of the previous cases, we found two patients had a history of chronic hepatitis B virus infection and cirrhosis, one patient had alcoholic cirrhosis and one patient had hepati-

Table 1. Summary of coexistence of hepatocellular carcinoma and renal cell carcinoma cases reported in the English literature

Author/ References	Patient Age/ Gender	Location	Hepatitis/cirrhosis	Clinical symptoms	Diagnosis	Treatment	Follow-up
Shetty [4] 2013	57 Y/M	Right lobe of the liver and Mid-pole right kidney	N/S	Asymptomatic	HCC and RCC	Right hepatectomy and Right radical nephrectomy	N/S
Lee [5] 2014	53 Y/M	Segment II of the liver and Left kidney	Alcoholic cirrhosis	General weakness	HCC and RCC	Radiofrequency ablation (RFA)	1-month
Gang [6] 2015	72 Y/M	Segment V of the liver and Lower pole of the left kidney	Hepatitis B and Cirrhosis	Incidental finding	HCC and RCC	RFA and Oral medication	8-month
Zhang [7] 2015	63 Y/M	Right hepatic posterior lobe and Lower portion of right kidney	Hepatitis B and Cirrhosis	Right upper quadrant abdominal pain	HCC (clear cell type) and RCC	Right hemihepatectomy and Partial wedge nephrectomy	6-month
Sun [8] 2016	42 Y/M	Left lateral hepatic lobe and Left kidney	Hepatitis B	Poor appetite and Abdominal discomfort	HCC and RCC	Left hemihepatectomy and Left nephrectomy	4-month
Current case	53 Y/M	Left lateral hepatic lobe and Lower portion of the right kidney	No	Incidental finding	HCC and RCC	Left hemihepatectomy and Right radical nephrectomy	18-month

Y, years; M, male; N/S, not specified; HCC, hepatocellular carcinoma; RCC, renal cell carcinoma.

tis B. Therefore, we hypothesized that chronic hepatitis B virus infection and cirrhosis may have served a crucial role in the development of coexistence of HCC and RCC. However, our patient had neither chronic hepatitis B virus infection and cirrhosis nor remarkable family history, we hypothesized the development of the tumors may has relationship with environmental and immunological factors.

Synchronous multiple malignancies are secondary lesions that present simultaneously or within 6 months following the development of the initial malignancy, and the probability of one lesion being a metastasis of the other must be excluded [10]. In the current case, the tumors were found simultaneously in his a routine medical examination, and histopathological analysis confirmed the malignant features of each tumor. The tumors were pathologically established as different types of cancer, with the tumor in the liver confirmed as HCC and the tumor in the kidney confirmed as clear cell renal cell carcinoma. The immunohistochemical staining results showed that neoplastic cells of the liver were positive for HepPar-1, GPC3, and negative for CD10 and Pax-8; however, renal neoplastic cells were positive for CD10 and Pax-8, but negative for the liver-derived markers Heppar-1 and GPC3. These findings support the diagnosis that the two types of cancer occurred in a random and synchronous manner.

The prognosis of patients with multiple primary cancers can be determined independently by the stage of each cancer [11]. Simultaneous removal of multiple primary cancers should be attempted, and adjuvant chemoradiation therapy treatment should also be considered. In the current case, the treatment of choice was curative resection of each cancer. According to Nzeako et al. [2], because of HCC is a tumor that is associated with poor survival and a more rapid progression than are most of the associated EHPM tumors, there is no significant difference in survival between patients with HCC and EHPM and those without EHPM. Kanematsu et al. [12] also noted that the cause of death were due to complications of the HCC and not to the EHPM. Thus, our patient was given the adiuvant chemoradiation therapy after operation, as the HCC tumor was particularly large (diameter, >10.0 cm). Currently, Radiofrequency ablation (RFA) is considered alternative in patients unable to undergo surgery [13]. According to review of the literature, 4 patients were treated by simultaneous removal of each tumor, and 2 patients were treated by RFA.

Conclusion

Synchronous double cancers of the liver and kidney are extremely rare, but the possibility of multiple primary cancers should be kept in mind during the preoperative examination. Especially, cirrhotics and chronic hepatitis B virus infection with HCC increased the risk of having an EHPM.

Disclosure of conflict of interest

None.

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