Clinical Case Report

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Small hepatocellular carcinoma suppressed by chemotherapy for synchronous gastric carcinoma after laparoscopy-assisted radical distal gastrectomy

A case report and literature review

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Abstract

Rationale: Synchronous gastric carcinoma and hepatocellular carcinoma (HCC) is rare. It is hard to distinguish synchronous HCC from metastatic liver cancer in this condition. The treatment and prognosis is quite different for synchronous HCC of gastric carcinoma and liver metastasis of gastric carcinoma.

Patient concerns: A 68-year-old man with a chief complaint of epigastric pain for 1 year, accompanied by reflux and belching. The patient was diagnosed with gastric carcinoma (cT4NxM0) and laparoscopy-assisted radical distal gastrectomy was performed. This was followed by chemotherapy of FOLFOX regimen. However, a liver nodule growth was observed after postoperative systemic treatment.

Diagnosis: The initial diagnosis was liver metastasis of gastric carcinoma. However after hepatectomy of segment VI and VII as well as thrombectomy of right hepatic vein, histology revealed intermediate to poor differentiated HCC. Hence this case was diagnosed as synchronous gastric carcinoma and HCC.

Interventions: A preventive transcatheter arterial chemoembolization (TACE) was conducted at 4 weeks after hepatectomy. Another FOLFOX regimen was suggested, but was refused by the patient.

Outcomes: The patient survived without tumor recurrence for 9 months after the second surgery.

Lessons: Synchronous HCC should be routinely distinguished from gastric carcinoma liver metastasis, especially for patients with hepatitis B virus (HBV) infection. The FOLFOX4 regimen for treating gastric carcinoma liver metastasis may have inhibited the progression of primary HCC in this case. This patient with HCC benefited from liver resection, inspite of hepatic vein tumor thrombosis.

Abbreviations: AFP = alpha-fetoprotein, GC = gastric cancer, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HMGC = hepatic metastasis from gastric cancer, MDT = multidisciplinary team, MRI = magnetic resonance images, TACE = transcatheter arterial chemoembolization.

Keywords: chemotherapy, gastric carcinoma, hepatectomy, hepatocellular carcinoma, synchronous carcinoma

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The authors have no conflicts of interest to declare.

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1. Introduction

Hepatocellular carcinoma (HCC) and gastric cancer (GC) are both common malignancies in Asia. Even though coexisted cancers are rare, the possibility of unrelated synchronous malignancies is supposed to be taken into consideration regardless of the prevalence. Particularly, GC patients with hepatitis B virus (HBV) infection background can present HCC as synchronous tumor at the same time, especially in area with high prevalence of HCC.

The management for synchronous HCC and GC requires simultaneous strategies.[1,2] Coinstantaneous surgery is recommended for double cancers regardless of primary tumor or metastatic malignancy, under the condition that tumors in both organs are surgically resectable.[1,2] The FOLFOX regimen was originally used to treat GC, but seemed to present certain suppressive effect on the synchronous small HCC at the same time in our case. Multidisciplinary team (MDT) meeting is newly proposed and strongly recommended from preoperative stage to later follow-up in hospital organization.

In the present report, a 68-year-old male patient was initially diagnosed as liver metastasis from gastric malignancy, but the

lesions in gastric antrum and liver turned out to be coincident GC and HCC, respectively. The patient seems to have benefited from FOLFOX regime initially by suppression of the HCC. We have obtained the approval from the patient to report the case.

2. Case presentation

A 68-year-old man with a chief complaint of epigastric pain for 1 year, accompanied by reflux and belch, was admitted to gastrointestinal surgery department in December, 2015. Two months before admission, he was feeling deterioration of disease and developed abdomen distension, which cannot be alleviated by Omeprazole. Other symptoms included fatigue, poor sleep quality, loss of appetite, and weight loss of 3 kg. He received appendectomy 20 years ago and other past medical history presented tuberculosis with regular treatment for 7 years, and average daily alcohol consumption for 350 mL in the past 10 years.

Laboratory data showed positive hepatitis B surface antigen (HBsAg), hepatitis B e antibody (HBeAb), and hepatitis B core antibody (HBcAb). Blood routine and biochemical, coagulation function, and tumor markers including CEA, CA19-9, and CA72-4 were within normal range. Abdominal computed tomography (CT) indicated antrum tumor with increasing lymph nodes in hepatogastric space, as well as a suspected small metastatic lesion in the right posterior lobe of the liver (Fig. 1). Gastric endoscopy showed advanced antrum tumor (Borrmann IV) and pyloric obstruction. Clinicopathology reported gastric adenocarcinoma. With the intraoperative diagnosis of gastric carcinoma (cT4NxM0), laparoscopy-assisted radical distal gastrectomy was performed. Resected specimens showed poor differentiated gastric adenocarcinoma invading entire gastric wall (Fig. 2A), together with lymph node metastasis at lesser curvature (8/17) and greater curvature (11/14). Cancer tissue was found in neither anastomotic stoma ends nor omentummajus. Immunohistochemistry staining presented pan-cytokeratin (+), epithelial membrane antigen (EMA) (+), cytokeratin 7 (+), cytokeratin 20 (+), caudal type homeobox gene 2 (+), Villin (+), Ki-67 (LI about 60–80%). The patient subsequently received the first time chemotherapy of FOLFOX regimen 20 days after operation, and 4 cycles of chemotherapy were followed. The patient could not adhere to the following cycles of FOLFOX regimen. However, the liver nodule has been growing after postoperative systemic treatment.

The patient was hospitalized again with complaint of anorexia and weakness for 3 months in May, 2017. Serum HBsAg, HBeAb, and HBcAb still remained positive. Hepatitis B virus-DNA quantitative was 4.09×10^3 cps/mL. Tumor markers were as following: alpha-fetoprotein (AFP) 84.35 ng/mL, CA19-9 46.58 U/mL, cytokeratin fragment 19 (CYFRA21-1) 6.05 ng/mL, and neuron-specific enolase 21.64 ng/mL. Gastric endoscopy showed no signs of gastric carcinoma recurrence. Computed tomography (CT) and magnetic resonance images (MRI) revealed parenchymal occupying lesion (15×10 cm) in the right lobe of liver, which could be explained by primary liver cancer; tumor thrombus in right hepatic vein was determined (Fig. 3). The patient underwent hepatectomy of segment VI and VII as well as thrombectomy of right hepatic vein. Histology revealed intermediate to poor differentiated HCC without microscopic vascular invasion (Fig. 2B and C); tumor tissue can be observed in right hepatic vein tissue. Immunohistochemistry reported the following: Hepatocyte (+), Glypican-3 (+), Arginasel (+), CD34 (vessels+), AFP (–), EMA (–), CK19 (–), Ki-67 (L1 about 50–60% at certain area).

A preventive transcatheter arterial chemoembolization (TACE) was conducted at 4 weeks after hepatectomy, and no recurrence or metastasis was found. Another FOLFOX regimen was suggested, but was refused by the patient. The patient did show serious adverse or unanticipated events. After 9 months following up, the patient survived without tumor recurrence (Fig. 4).

3. Discussion

Synchronous gastric carcinoma and HCC are rare. We found 20 reports on coincident GC and HCC between 1988 and 2016, through literature search on PubMed (Table 1).

Almost all of them received simultaneous resection of gastric and liver lesions. Some of them followed adjuvant or neoadjuvant chemotherapy as S-1 or S-1 plus cisplatin (CDDP). Only a few of them reported prognosis which was not very optimistic.

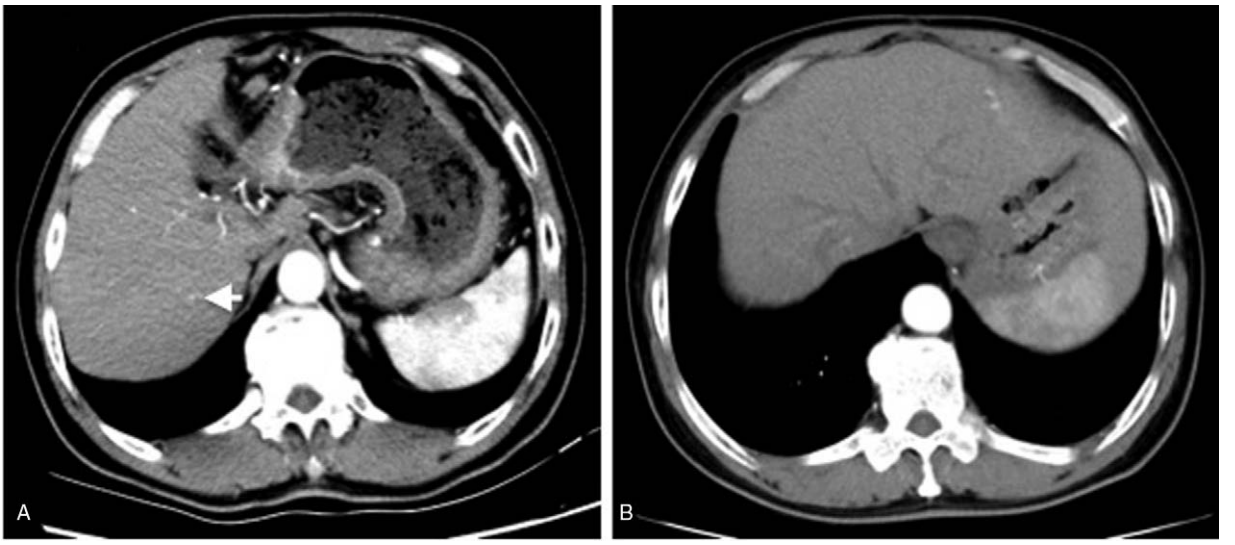

Figure 1. Enhanced abdominal CT scanning indicated lesion (arrow) in the right posterior lobe of the liver and antrum tumor with increasing lymph nodes in hepatogastric space (A). The hepatic veins did not show tumor thrombosis (B). CT = computed tomography.

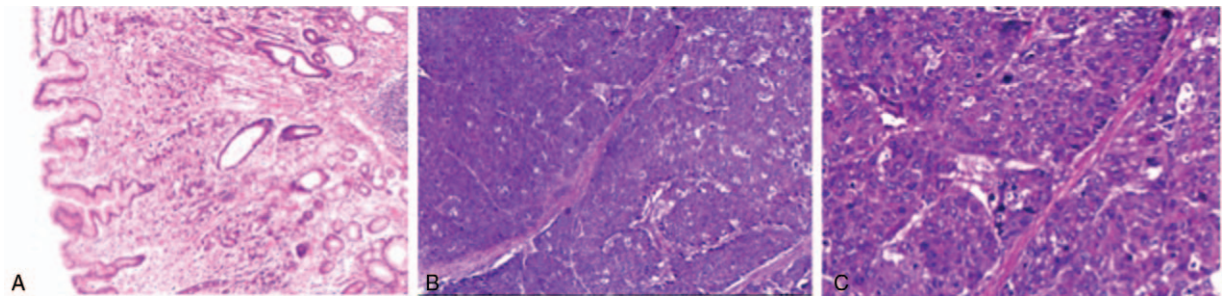

Figure 2. Pathological examination showed poor differentiated gastric adenocarcinoma invading entire gastric wall after distal gastrectomy (A) and intermediate to poor differentiated HCC without microscopic vascular invasion after liver resection (B and C). HCC = hepatocellular carcinoma.

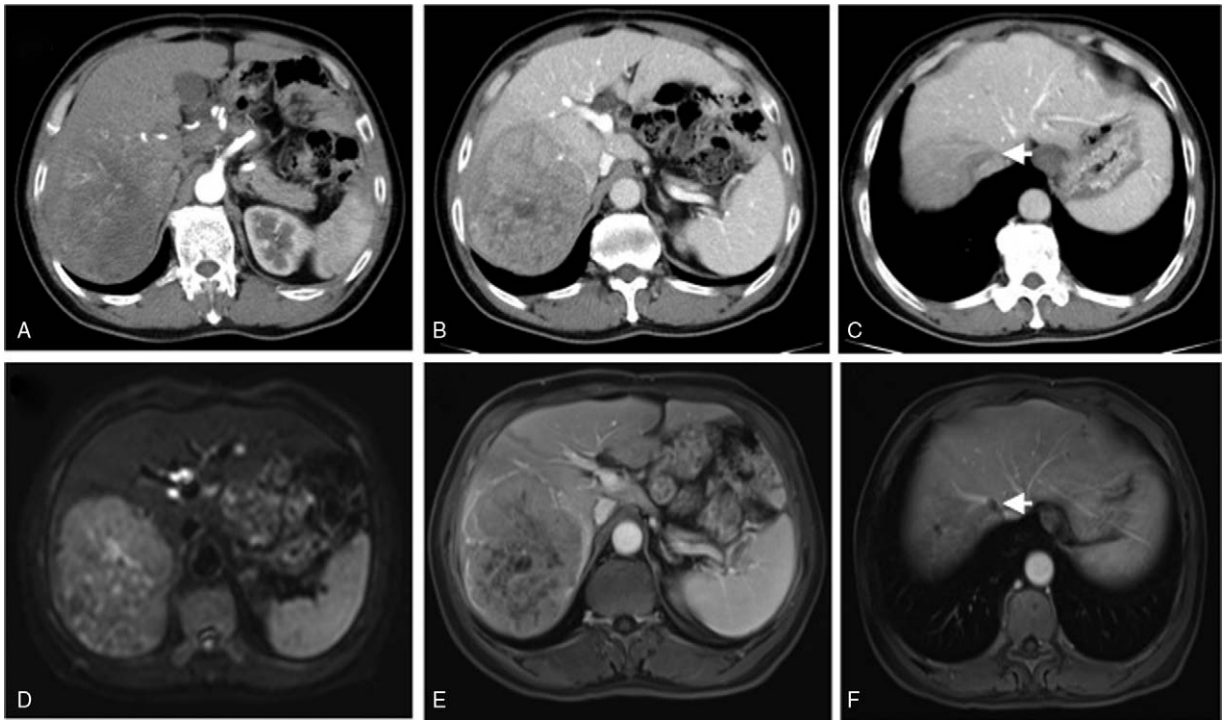

Figure 3. CT and MRI revealed parenchymal occupying lesion (15 × 10 cm) in the right lobe of liver, which could be explained by primary liver cancer (A and D); tumor thrombus was not detected in the portal vein (B and E), but was determined in right hepatic vein (C and F). CT = computed tomography, MRI = magnetic resonance imaging.

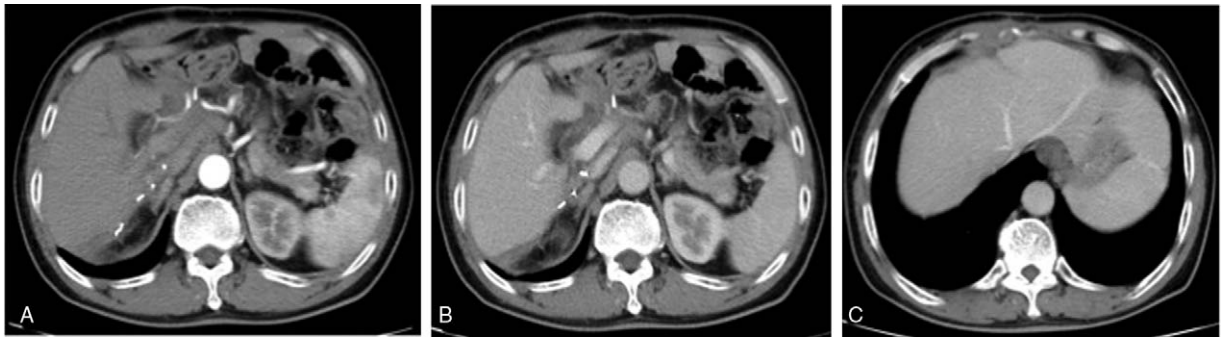

Figure 4. Enhanced CT scanning was performed 6 months after liver resection. No tumor recurrence was detected in the hepatic parenchyma (A and B) or hepatic vein (C). CT = computed tomography.

Table 1

Representive reports of coincident GC and HCC between 1988 and 2016.

No	Author	Journal	Year	Cancer	Case	Surgery/Treatment
1	Ajiki T[1]	Gan To Kagaku Ryoho	2016	GC + HCC	1	Simultaneous laparoscopic distal gastrectomy + partial liver resection
2	Mizuno T[3]	Gan To Kagaku Ryoho	2016	GC + HCC	1	Endoscopic submucosal dissection for early GC + curative resection for HCC
3	Ferreria E Mora H[4]	Int J Surg Case Rep	2015	Gastric GIST + HCC	1	Gastrotomy + left liver ultrasound guided lobectomy
4	Omura N[5]	Gan To Kagaku Ryoho	2013	GC + HCC + bladder cancer + urothelial carcinoma	1	Semi-total gastrectomy + partial hepatectomy-S6 + radio frequency ablation-S5/7 + cholecystectomy
5	Banumathi Ramakrishna[6]	J Gastrointest Cancer	2012	GC + HCC	1	Distal gastrectomy + left lateral segmentectomy
6	Chong VH[7]	Singapore Med J	2010	GC + HCC + large B cell lymphoma	1	Billroth II gastrectomy for gastric adenocarcinoma 13 years ago + biopsies + no specific therapy
7	Oka T[8]	Gan To Kagaku Ryoho	2009	GC + HCC	1	Neoadjuvant chemotherapy (S-1/CDDP) + surgical resection for GC + HCC (distal gastrectomy + D2 + lymph node excision + S5 segmentectomy + cholecystectomy)
8	Mircea Cazacu[9]	Journal of Radiotherapy & Medical Oncology	2009	GC + HCC + right thigh sarcoma	1	Gastrectomy with eso-jejunal precolic terminallateral anastomosis with Braun anastomosis, jejunostomy and wedge resection of the liver tumor
9	Ewertsen C[10]	BMJ Case Rep	2009	gastric NEC + HCC	1	NA
10	Kawada J[11]	Gan To Kagaku Ryoho	2008	GC + HCC + rectal cancer	1	TACE; 2. Rectal cancer resection; 3. TACE*3; 4. Partial hepatectomy + distal gastrectomy simultaneously
11	Ha TK[12]	Yonsei Med J	2007	GC + HCC	13	Total/distal gastrectomy + enucleation/intraoperative radiofrequency ablation/lobectomy/sectionectomy
12	Wong LL[13]	Hawaii Med J	2007	GC + HCC	1	NA
13	Goutallier BF[14]	Tunis Med	2006	GC + HCC	1	NA
14	Terakura M[15]	Gan To Kagaku Ryoho	2005	GC + liver and lymph metastases + HCC	1	Distal gastrectomy + TS-1 + HAI of low-dose CDDP
15	Chang JY[16]	Korean J Intern Med	2003	GC + HCC + cholangiocarcinoma	1	Left lobectomy + wedge resection in right lobe + subtotal gastrectomy
16	Uenishi T[2]	Dig Surg	2003	GC + HCC	13	Curative surgery for HCC + GC
17	Koide N[17]	Hepatogastroenterology	1999	GC + HCC	10	Early GC: limited gastric resection + curative HCC surgery; advanced GC: curative gastrectomy with lymphadenectomy
18	Chen CN[18]	Hepatogastroenterology	1998	GC + HCC	7	Synchronous hepatectomy + radical gastrecctomy
19	Takayasu K[19]	Cancer	1992	GC + HCC	7	NA
20	Ng BL[20]	Ann Acad Med Singapore	1988	GC + HCC	1	Resection at one operation

GIST = gastrointestinal stromal tumor, HAI = hepatic arterial infusion, NA = not applicable, NEC = gastric neuroendocrine carcinoma.

The diagnosis of coincident gastric and liver malignancy was not difficult to make when keeping in mind that gastric cancer patients with HBV infection background can present HCC as synchronous tumor at the same time, especially in area with high prevalence of HCC. However, in this case, we did not consider the possibility of synchronous primary liver cancer at the first admission. Even after the preoperative routine image examinations including ultrasound and CT, we still regarded the small tumor in liver as metastatic lesion from gastric cancer instead of primary liver malignancy.

In our case, the patient received standard FOLFOX regimen chemotherapy for 4 cycles after laparoscopy-assisted radical distal gastrectomy with no complaint of obvious intolerance symptoms. The antrum malignancy has been resolved by FOLFOX chemotherapy according to the follow up records. Meanwhile, the FOLFOX regimen seemed to present valid suppressive effect on the synchronous small hepatocellular carcinoma, as the liver lesion was stable (standard deviation [SD] for 3 months) during chemotherapy but progressed immediately after treatment. Based on this observation, we discussed the potential impact of FOLFOX and other chemotherapy regimens on HCC in this report.

Standard FOLFOX regimen is composed of leucovorin (Folinic acid), 5-fluorouracil (5-FU), and oxaliplatin, which has been widely used in treating colorectal cancer and related metastatic cancer.[21–23] A number of randomized controlled trial researches have also exhibited special interests resectable or unresectable liver metastases from colorectal cancer. However, there is not much concern about FOLFOX regimen on primary hepatic cancer. One of the explanations might be that HCC patients, unlike other solid tumors, are not treated with systemic chemotherapy in routine since HCC is considered highly refractory to chemotherapy and other systemic therapy.[22,24]

Oxaliplatin is a platinum-based cytotoxic agent which presents active effect among colorectal carcinoma and several cisplatin-resistant cell lines and solid tumors. 5-FU is reported to play an anti-proliferative role in regulating cell cycle progression by increasing S-phase fraction. Evidences showed that both oxaliplatin and 5-FU may have anti-cancer effect on HCC in basic research.[25–27]

Therefore, we think the major elements, Oxaliplatin and 5-FU, in FOLFOX regimen possess potential application prospect in management of HCC, even though the widely accepted notion

goes that HCC is resistant to chemotherapy.[22,24,28–30] Further, Oxaliplatin and 5-FU can benefit not only HCC patients in advanced stage as evaluated in several clinical studies before, but also in early stage cases like what we reported herein. However, further researches and clinical trials are still under investigation.

From the surgical point of view, the coincident liver tumor was supposed be treated at the first surgery, regardless of whether it originated from liver in situ or metastasized from antrum.

The beneficial effect of hepatectomy for hepatic metastasis from gastric cancer (HMGC) has not been well-established. In a review of surgical resection of hepatic metastasis from gastric cancer by Kodera et al,[31] indication for surgery included the number of metastatic nodules, unilobular distribution, solitary tumor, tumor diameter, and capsular formation regarding hepatic tumor. For HMGC with 3 or fewer metastatic nodules, surgery was currently considered by Takemura et al,[32] who had reported a 5-year survival of 37% in HMGC patients before. Fausto Petrelli et al[33] systematically evaluated literatures of hepatic resection for HMGC and concluded that surgical resection can obtain acceptable 5-year overall survival particularly after metachronous lesion resection in selected patients.

Even without consideration of the special synchronous situation, the small liver tumor should be treated anyway. The liver tumor incidentally found in perioperative examination of GC provided us with a rare opportunity to take step, which made it possible to obtain promising therapeutic effect in this symptomless case of very early stage HCC. Because in most cases, the HCC has already developed into advanced stages at the time of diagnosis, and the prognosis of HCC is not very optimistic with 5-year survival >70% in early diagnosis and <16% in late diagnosis, respectively. According to Dusheiko[34] review on Lancet in 1992, small tumors are "amenable" to treatment whether resectable or not. Even though better prognosis obtained in small tumor identified by screening might the result of "lead time bias," there were still several treatments potential to improve prognosis or palliation. Cauchy et al[35–38] concluded 3 studies from Zhong et al[35], Sasaki et al[37], and Thomasset et al[36] in World Journal of Surgery and thought oncologic risk of isolated small lesion was underestimated. Only for patients without severe underlying parenchymal lesion, locoregional or resectional therapies and liver transplantation might be able to achieve similar outcomes. Based on our observation and analysis, we have reasons to believe that the patient could achieve a better outcome with simultaneous surgery for simultaneous gastric carcinoma and liver tumor at the first diagnosis.

This case provided a lesson for clinicians in the following aspects. First, MRI should be routinely done for patients with gastric cancer to exclude liver metastasis or synchronous hepatic carcinoma. In this case, MRI examination would provide more information to distinguish liver cancer at the first clinical visit. Second, patients should be followed up strictly according to physicians' recommendations. The patient in this case did not adhere to chemotherapy schedule and clinic visit after systemic treatment. At the time he was hospitalized again with complaint of anorexia and weakness, the liver carcinoma had developed with tumor thrombosis in the hepatic vein, indicating poor prognosis.

At the same time, we should also attach importance to lifelong anti-HBV therapy in HCC patient with chronic hepatitis B virus infection, especially those with active HBV replication. Entecavir, Telbivudine, and Tenofovir are potential drugs of options with strong effect but less resistance. Further, HCC patients can be accompanied by abnormal liver function, which demands appropriate application of hepatoprotective, cholagogue, and anti-inflammation drugs to improve the general situation.

We suggest regular multidisciplinary team (MDT) meeting in clinical work, since the patient in our case might have obtained better prognosis if simultaneous curative treatment of gastric cancer and hepatic malignancy was given by gastric and hepatic surgeons together with oncologists, pathologists, radiologists, and other professions at the first admission.

MDT meeting might be a solution to make up the gap between medical professionals, which is highly demanded for proper management of patients. National health service has introduced MDT for cancer managing and evaluation since 2007, and hepatic surgery center in Tongji Hospital applied it in clinical practice after 2013. Different from traditional consultation aiming at handling discovered problems, MDT emphasized on the regular time, position, and participants in order to catch sight of new problems at early stage or even rectify the referral diagnoses. Basta et al[39] analyzed 551 consecutive patients in 74 gastrointestinal oncology MDT meetings with a total of 691 times, prospectively. The result showed 20% of rectified referral diagnoses, especially with presence of treating physicians. According to our own experience and reports, we suggest regular MDT meeting in malignancy management.

Author contributions

Conceptualization: Binhao Zhang.
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Formal analysis: Chao Wang.
Funding acquisition: Binhao Zhang.
Investigation: Chao Leng.
Methodology: Chao Wang, Xin Luo, Shui-Lin Dong, Chao Leng, Binhao Zhang.
Resources: Chao Wang, Binhao Zhang.
Supervision: Bi-Xiang Zhang, Binhao Zhang.
Validation: Xin Luo, Chao Leng.
Writing – original draft: Chao Wang.
Writing – review & editing: Bi-Xiang Zhang, Binhao Zhang.

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