

Laparoscopic Surgery for a Patient With Multiple Liver Metastases of Unknown Origin Concomitant With Gallbladder Tumor

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Abstract. *Background: The liver is the digestive organ where metastatic adenocarcinoma of unknown primary site is most often observed. Case Report: A 74-year-old man was diagnosed with a growing gallbladder tumor and multiple liver tumors limited to the left lateral sector. Liver tumors were suggested to be primary or secondary adenocarcinoma with no relation to the gallbladder tumor. Also for diagnostic purposes, laparoscopic full-thickness resection of the gallbladder, laparoscopic lateral sectionectomy and lymph node sampling were performed. The final histopathological diagnosis was hyperplastic polyp of the gallbladder and metastatic poorly differentiated adenocarcinoma of the liver. Liver tumors were suspected to originate from the stomach, duodenum, or small intestine; however, the primary sites could not be identified. The patient has been closely followed up without any chemotherapy 3 months after surgery. Conclusion: Laparoscopic surgery can be strongly recommended for patients with multiple liver tumors of unknown origin concomitant with a gallbladder tumor.*

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Key Words: cancer of unknown primary site, liver metastases of unknown primary site, metastatic adenocarcinoma, gallbladder tumor, laparoscopic surgery.

Cancer of unknown primary site (CUP) is defined as histopathologically confirmed metastatic cancer with undiagnosed primary lesion and consists of heterogeneous features accounting for 3%-5% of all cancers (1, 2). In patients with CUP, the primary tumor can regress or stay dormant, and some malignant cells will metastasize to secondary sites early on.

Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and other tumor types occur primarily in the liver (3, 4). Additionally, the liver is a well-known metastatic site of malignant tumors that spread through not only the portal but also the systemic circulation (5, 6). Liver metastases from gallbladder cancer are often observed adjacent to the gallbladder, especially in the perfusion area of the cystic vein, so gallbladder bed resection has been performed for potential liver metastases (7, 8). Liver metastases from prostate cancer are regularly observed among patients with multiple organ metastases (9).

In patients with liver metastases, to identify the primary site, various assessments are required, including patient history, serum tumor markers, detailed diagnostic imaging, as well as histopathological examination (10, 11). Metastatic adenocarcinoma is the most common CUP. The primary site of approximately one-third of patients of metastatic adenocarcinoma of unknown primary site (MACUP) has been identified in a digestive organ (10). Occurrence in digestive organs is significantly linked with liver [odds ratio (OR)=13.21, $p<0.001$] or lung (OR=2.36, $p=0.001$) metastases (10).

In the differential diagnosis of liver tumors, contrast-enhanced ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI) are often used. Furthermore, some functional images are necessary,

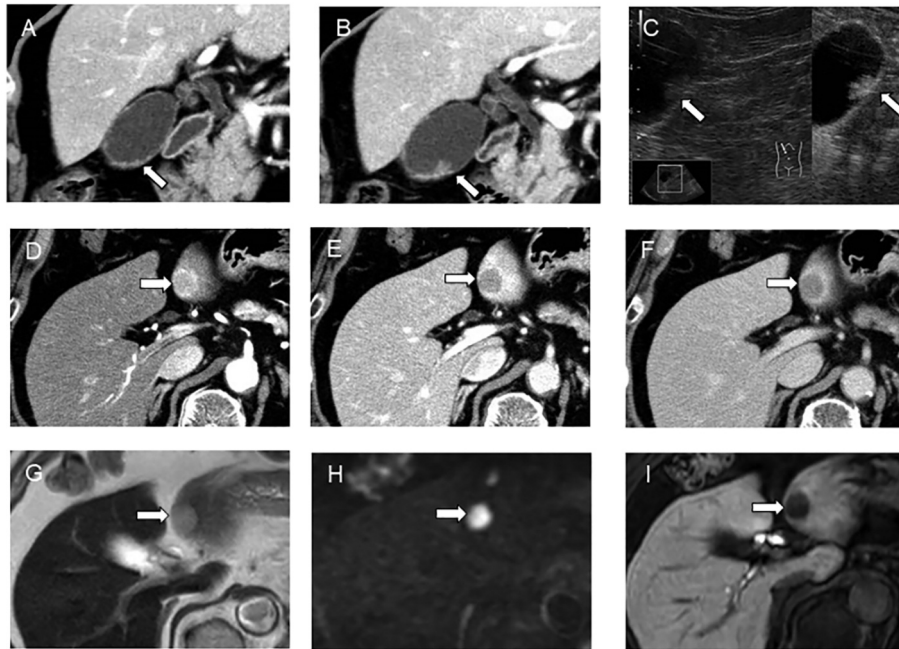


Figure 1. Preoperative diagnostic images. Contrast-enhanced computed tomography (CT) coronal images in the portal venous phase showing the gallbladder tumor that tended to increase in diameter (A, B). Contrast-enhanced ultrasonography shows a mulberry-type enhanced lesion in the gallbladder on the vascular phase (C). Abdominal CT images of the liver tumor (D-F). The tumor showed an early ringed enhancement (D) with prolonged peripheral enhancement (E, F) during the arterial phase to equilibrium phases. Magnetic resonance (MR) images (G-I). T2-weighted MR image shows a mildly hyperintense tumor in the lateral segment (G). Diffusion-weighted image shows hyperintensity; the mean apparent diffusion coefficient was calculated as $1.1 \times 10^{-3} \text{ mm}^2/\text{s}$ (H). Gadolinium-ethoxybenzyl-diethylenetriamine pentaacetate MR images of the hepatobiliary phase are hypointense (I). Tumor is indicated by an arrow.

including diffusion-weighted and hepato-specific MRI and nuclear metabolic imaging using positron emission tomography (PET)/CT (12). Assessment of biomarker levels including serum tumor markers is beneficial in identifying the primary origin of liver tumors (13, 14).

For patients with liver metastases, a large number of liver metastases is a predictor of poor prognosis after hepatectomy (15). Limited to colorectal origin, for patients with ≥ 5 liver metastases, upfront hepatectomy is not optimal and neoadjuvant chemotherapy is recommended (16, 17). Liver metastases are one of the poor prognostic factors in patients with gallbladder cancer (18). However, advances in novel chemotherapy can make such patients live longer than the past (19-21).

Herein, we report a patient with liver metastases (five lesions) from CUP limited in the left lateral sector of the liver concomitant with a growing gallbladder tumor, who was successfully treated with laparoscopic surgery.

Case Report

A 74-year-old man had been undergoing follow-up for gallbladder adenomyomatosis since 2020. In the same year, he started hormone therapy for advanced prostate cancer.

Contrast-enhanced CT with a 6-month interval showed that the gallbladder lesion had a broad base and tended to increase in diameter (10 mm to 18 mm), and the entire lesion was markedly contrast-enhanced, suggesting gallbladder cancer (Figure 1A, B). The tumor was similarly well-enhanced with contrast-enhanced ultrasonography (US) (Figure 1C). At the same time, 5 hepatic mass lesions with ringed enhancement were observed limited in the lateral sector and were mostly suggested to be primary or secondly adenocarcinoma (Figure 1D-I). Liver tumors were determined as having a low possibility of metastases from gallbladder cancer based on their distribution. Carcinoembryonic antigen (CEA), carbohydrate antigen (CA19-9), and α -fetoprotein levels were within normal range. The level of protein induced by vitamin K absence or antagonist-II was high (17,021 mAU/ml), possibly due to warfarin administration for atrial fibrillation. Prostate-specific antigen (PSA) was also within normal levels, so liver metastasis from prostate cancer was considered unlikely. Upper and lower gastrointestinal endoscopy showed no abnormalities. Other diagnostic images did not show lesions corresponding to the primary site of liver metastases. As a diagnostic treatment, laparoscopic surgery was performed.

On laparoscopic observation, no obvious lesions corresponding to the primary site of liver metastases were

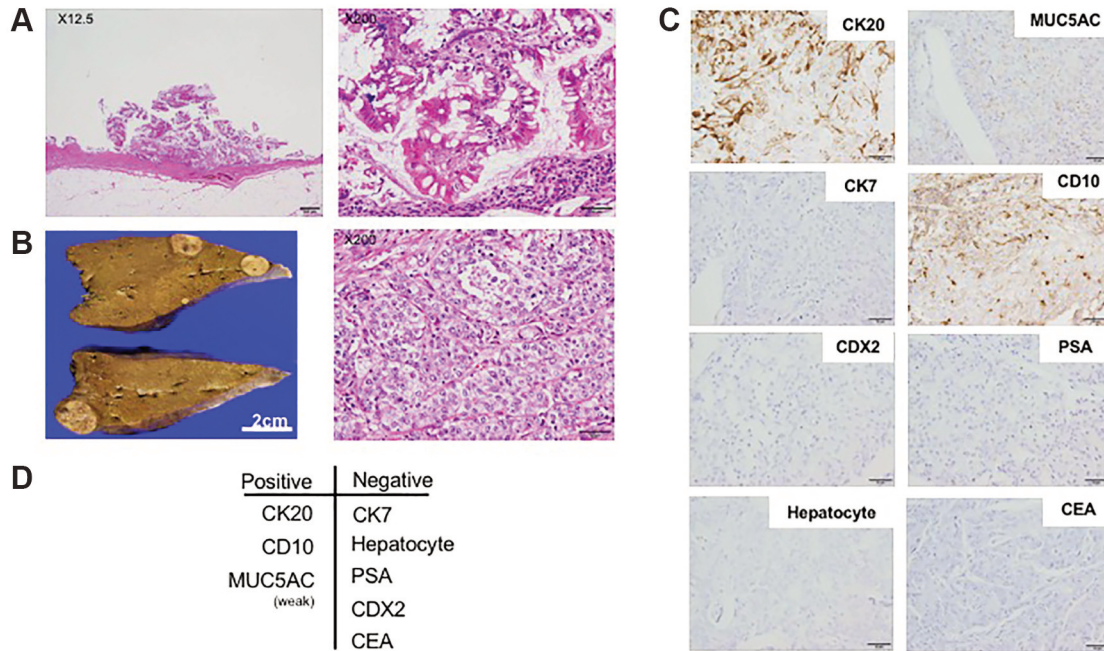


Figure 2. Histopathology-related images. (A) Hematoxylin-eosin staining shows a 5-mm polypoid lesion on the mucosal wall surface of the gallbladder. Goblet and columnar cells without atypia grew and formed papillary structures. (B) Some well-circumscribed masses were detected in the liver. (C) Liver tumors were positive for CK20, CD10 and MUC5AC and negative for CK7, hepatocytes, prostate-specific (PSA) antigen, CDK2, and carcinoembryonic antigen (CEA). (D) Summary of the immunohistochemistry.

found. Laparoscopic echo showed a well-preserved layered structure of the gallbladder wall, so early-stage gallbladder cancer or non-cancerous polyp was suspected. Laparoscopic full-thickness resection of the gallbladder (cholecystectomy inclusive of the cystic plate) and laparoscopic lateral segment resection were performed. Sampling of peri-cystic-duct and peri-bile-duct lymph node was also performed. The operative time was 343 min with a blood loss of 50 grams. Gross examination of the resected specimen showed no obvious malignant findings on the mucosal surface of the gallbladder and multiple white nodules of elastic hardness were found in the liver. With histopathological examination, polypoid lesion of the gallbladder was diagnosed as a hyperplastic polyp (Figure 2A). Some whitish and well-circumscribed masses of 2-20 mm were detected in the liver (Figure 2B). Each nodule in multiple liver lesions showed similar histological features; neoplastic cells with eosinophilic cytoplasm formed a solid nest with an irregular glandular structure. Liver lesions appeared to be poorly differentiated HCC in hematoxylin-eosin stained sections; however, HCC and ICC were excluded based on results of precise immunohistochemistry (Figure 2C). Liver tumors were positive for CK20, CD10 and MUC5AC and negative for CK7, hepatocyte, PSA, CDK2 and CEA (Figure 2D). This immune phenotype suggested the liver tumors were poorly differentiated adenocarcinoma that originated from the stomach, duodenum or small intestine (10, 22, 23).

The postoperative course was good and the patient was discharged on the 10th day after surgery. PET-CT was performed 1 month after surgery, but no obvious primary site was identified. Small intestine fluoroscopy showed no abnormality. We plan to examine the patient through strict follow-up without any systemic chemotherapy. The patient is currently alive with no new lesions 3 months after surgery.

Discussion

We encountered a patient with liver metastases of unknown origin concomitant with a gallbladder tumor suspected of being malignant and was synchronously treated with the laparoscopic approach. From the preoperative diagnostic images, the irregular border and ringed-enhanced liver tumors were suspected as ICC or liver metastases of adenocarcinoma; they were determined as having a low possibility of liver metastases from gallbladder cancer, based on their distribution (24, 25). Liver metastases from the prostate were excluded because of the stable condition of prostate cancer and normal PSA levels. No other suspicious primary lesion was detected perioperatively.

In fact, multiple liver metastases from the gallbladder and prostate are a contraindication of liver resection (7-9). A large number of liver metastases and lymph node metastases are considered poor postoperative prognostic factors of ICC,

but ICCs with such factors were not contraindicative of liver resection (26, 27). Recently, some therapeutic regimens have been developed as an adjuvant therapy after liver resection (28, 29). Percutaneous US-guided needle biopsy of a liver tumor is one of the options to obtain histopathological diagnosis. However, needle biopsy is not recommended for highly malignant liver tumors like ICC due to the risk of intra-abdominal dissemination (30).

Histopathologically, the gallbladder tumor was diagnosed as a benign hyperplastic polyp. Based on the results of immunochemical staining, the liver tumor was diagnosed as poorly differentiated adenocarcinoma, highly suspected of liver metastases from the stomach, duodenum or small intestine (10, 22, 23). However, postoperative whole-body PET/CT and small intestine fluoroscopy showed no suspicious primary lesion. A meta-analysis of PET/CT for patients with CUP demonstrated a primary tumor detection rate of 37% (31). At present, our patient is diagnosed with MACUP.

Laparoscopic liver resection has been widely adopted as a less invasive alternative to open liver resection (32, 33). For malignant liver tumors, laparoscopic liver resection can provide better short-term results and at least similar long-term prognosis (33-35). More specifically, left lateral sectionectomy is a commonly performed procedure. Laparoscopic cholecystectomy is the most common laparoscopic procedure, and laparoscopic full-thickness cholecystectomy was developed for low-grade malignant or suspicious malignant gallbladder lesions (36). For our patient, laparoscopic observation and US to detect the primary site and peritoneal dissemination, full-thickness cholecystectomy, lymph node sampling and liver resection were simultaneously performed.

Adenocarcinoma metastasis to the liver, especially of the poorly differentiated type, is classified as an unfavorable subset (2). Patients in whom liver resection is not possible are mainly treated with chemotherapy using platinum- and/or taxane-containing regimens (11, 37). Fortunately, our patient showed metastases limited to the liver and postoperative PET/CT demonstrated no suspicious malignant lesion; therefore, he has been followed up without any chemotherapy. If recurrence occurs, one of the aforementioned chemotherapy methods can be employed.

In conclusion, laparoscopic surgery is strongly recommended as a diagnostic treatment for liver tumors of unknown origin to achieve detailed histopathological examination. Further various laparoscopic investigations and treatments can be performed in combination.

Conflicts of Interest

All Authors have no conflicts of interest to declare in relation to this article.

Authors' Contributions

Manuscript writing: Beppu T, Hara Y, Yamamura K. Substantial contributions to conception: Matsumura K, Tomiguchi J, Motohara T, Miyamaoto H. Technical support and interpretation: Beppu T, Hara Y, Yamamura K, Yuki H, Oda E, Akahoshi S. Histopathological diagnosis: Komohara Y.

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Received May 19, 2021
Revised June 9, 2021
Accepted June 11, 2021