Clinical Case Report

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A case report of cholangiocarcinoma combined with moderately differentiated gastric adenocarcinoma

Yan-Hui Yang, MD, PhD[a], Qing Deng, MD[b], Tian-Bao Yang, MD[a], Yang Gui, MD[a], Yu-xiang Zhang, MD[c], Jiang-Bo Liu, MD, PhD[d], Qian Deng, MD[e], Wei-Feng Liu, MD[a], Jun-Jun Sun, MD[a,*]

Abstract

Rationale: Multiple primary carcinoma (MPM) refers to simultaneous or successive occurrence of ≥2 types of primary malignant tumors in a single organ or in different organs of the same individual. It is rarely seen in clinical practice. Among the various types of MPM, hilar cholangiocarcinoma combined with gastric cancer is extremely rare.

Patient concerns: The patient was a 61-year-old man who was admitted to our hospital due to upper abdominal discomfort and yellow-stained skin mucosa for 9 days.

Diagnoses: Preoperative diagnosis: Considering the typical preoperative painless jaundice as well as his clinical imaging report, the patient received the following preoperative diagnosis: obstructive jaundice, type IV hilar cholangiocarcinoma based on Bismuth-Corlette classification, and no intrahepatic distant metastasis. Intraoperative diagnosis: The results of intraoperative snap freezing and laboratory examination indicated gastric adenocarcinoma. Therefore, the patient received an intraoperative diagnosis of obstructive jaundice, hilar cholangiocarcinoma, and gastric cancer. Postoperative pathological diagnosis: Postoperative pathological examination of the gastric lesion revealed the following results: ulcerative, moderately differentiated gastric adenocarcinoma and intestinal type in the Lauren classification of stomach cancer; moderately differentiated adenocarcinoma of the bile duct.

Interventions: Surgical resection operation was carried out and the patient received chemotherapy after operation. But we could not strictly follow the relevant clinical guidelines to perform standardized operations and provide comprehensive treatment because of his economic situation, psychological factors, and the current medical environment in China.

Outcomes: The patient did not receive standardized postoperative therapy. Although he lived and worked normally for 8 months after the operation, he died 10 months after surgery.

Lessons: This report reminds us to pay close attention to the likelihood of MPM and other low-incidence diseases. The physicians and imaging clinicians should explore all clinical possibilities to avoid misdiagnosis of this rare disease and formulate effective treatment plans to maximize the therapeutic benefits for the patient.

Abbreviations: ALT = alanine transaminase, AST = aspartate aminotransferase, CA = carbohydrate antigen, CD = cluster of differentiation, CDx = Caudal type homeobox, CEA = carcinoembryonic antigen, CgA = chromogranin, CK = cytokeratin, CT = computed tomography, HER-2 = human epidermal growth factor receptor-2, MPM = multiple primary carcinoma, NSE = neuron specific enolase, Syn = synaptophysin.

Keywords: cholangiocarcinoma, gastric adenocarcinoma, misdiagnosis, multiple primary carcinoma

1. Introduction

In 1889, Billroth[1] described multiple primary carcinoma (MPM) for the first time. Later, in 1932, Warren and Gates compiled 1259 case reports[2] and subsequently defined MPM as the concurrent or consecutive occurrence of no <2 independent primary malignant tumors, which may emerge in different systems and organs (paired organs or single organs), meeting the

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The Patient's Perspective and Informed Consent: After the operation, the patient was satisfied with the outcome of our treatment. At the first and second outpatient visits, however, he rejected our recommendation of chemotherapy for economic reasons and due to psychological aversion. During a follow-up visit, the informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

[a] Department of Hepatobiliary Surgery, [b] Department of Pathology, [c] Department of Urology Surgery, [d] Department of Breast Surgery, First Affiliated Hospital, College of Clinical Medicine, Henan University of Science and Technology, [e] Faculty of Pharmaceutical Sciences, Luoyang Central Hospital affiliated to Zhengzhou University, Luoyang, China.

[*] Correspondence: Jun-Jun Sun, Jinghua Road No. 24, Luoyang, 471003, China (e-mail: doctjsun@163.com).

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following 3 criteria: each tumor must be established as malignant based on pathological examination; constituent tumors must have different histologic traits; and the possibility of recurrence or metastasis is excluded. This definition is still used today. According to the timing of diagnosis for each constituent tumor, MPMs are classified into 2 categories: they are called synchronous MPMs if constituent tumors emerge simultaneously or within 6 months; otherwise, they are called heterochronous MPMs.[3] MPM is often overlooked or misdiagnosed because of the low incidence and atypical clinical symptoms. MPM cases reported in the literature mostly involve tumors of different organs in a same system or tumors with different histologic types in a same organ.[4–7] This particular case involved a patient with synchronous MPM comprising cholangiocarcinoma and gastric adenocarcinoma. Curation of the literature retrieved no report of such a case. This article examines the clinical features of this case, reports the diagnosis and treatment process, and presents a corresponding literature review.

2. Case report

The patient was a 61-year-old man who was admitted to the Department of Hepatobiliary Surgery of our hospital due to "upper abdominal discomfort and yellow-stained skin mucosa for 9 days." Nine days prior to admission, the patient developed upper abdominal discomfort, mainly located under the xiphoid process and causing persistent dull pain, without any obvious cause. The condition, which was not related to food consumption, manifested a series of symptoms including mild yellow staining of the skin mucosa, a deep urine color, anorexia, and nausea, but the patient did not have obvious acid regurgitation, heartburn, or dietary choking. Hepatic function examination at a local clinic revealed the following results: alanine transaminase (ALT) 469 U/L, aspartate aminotransferase (AST) 482 U/L, total bilirubin 34.45 μmol/L, direct bilirubin 11.42 μmol/L, and indirect bilirubin 24.03 μmol/L. Therefore, the patient received treatments for gastritis, including acid suppression and gastrointestinal pro-peristaltic medications, but these led to no obvious mitigation of abdominal pain and jaundice. Four days prior to admission, the patient developed progressive aggravation of systemic yellow staining on the skin mucosa without any apparent cause. He went to a local county hospital, where he underwent abdominal computed tomography (CT), which yielded the following results: dilatation of the intrahepatic bile ducts, shadows in the hilar soft tissue, and irregular thickening of the stomach wall. For further therapy, the patient was transferred to our hospital on April 1, 2017. After admission, hepatic function examination revealed the following results: ALT 550 U/L, AST 309 U/L, total bilirubin 322.6 μmol/L, direct bilirubin 234.7 μmol/L, and indirect bilirubin 87.9 μmol/L; examination of tumor biomarkers yielded the following results: carbohydrate antigen 199 (CA199) 320.50 U/mL, with carcinoembryonic antigen (CEA) and carbohydrate antigen 125 (CA125) both in the normal ranges. Plain and contrast-enhanced CT scans in the upper abdomen showed the following results: space-occupying lesions in the common hepatic duct and left hepatic duct indicative of cancer, obstructive dilation of the intrahepatic and extrahepatic bile ducts, thickening of the duodenal bulb, and postprandial gallbladder manifestations (CT images shown in Fig. 1). Cardiac color ultrasound showed the following results: mild tricuspid regurgitation, decreased left ventricular diastolic function, and an ejection fraction of 59%. Pulmonary function tests yielded the following results: mild obstructive pulmonary ventilation dysfunction and a lung ventilation reserve volume of 92%. The patient had a prior history of being healthy with no diseases. Among his family members, his father had died of cardiac cancer.

The short strips of the confluence of the hepatic ducts were obviously strengthened in the arterial phase, and the irregular thickening of the stomach wall was obviously strengthened.

Considering the series of clinical signs, including typical preoperative painless jaundice, a direct bilirubin level of 234.7 μmol/L, and a CA199 level of 320.50 U/mL, as well as his clinical imaging report, the patient received the following preoperative diagnosis: obstructive jaundice, type IV hilar cholangiocarcinoma based on Bismuth-Corlette classification, and no intrahepatic distant metastasis. Surgical excision was considered, which was expected to lead to R0 resection.

After implementing measures to protect the liver, improve nutritional status, and exclude surgical contraindications, the patient underwent surgery under general anesthesia on April 7, 2017. Routine intraoperative exploration of the abdominal cavity revealed the following findings: extensive yellow staining was present across the abdominal viscera; an irregular hard mass in the common hepatic duct was present between the left and right branches of the hepatic portal vein, which invaded into the portal vein, the left and right hepatic ducts, the intrahepatic bile ducts, and part of the liver tissue; the hepatic duct exhibited local thickening, a hard texture, and complete blockage in the lumen; multiple enlarged lymph nodes with a hard texture were found in the hepatoduodenal ligament and upper edge of the pancreas; a 4 cm × 5 cm hard mass was present in the cardiac side of the stomach; and multiple enlarged lymph nodes were present around the stomach. At this point, the preoperative contrast-enhanced CT images (Fig. 1) were revisited, which in conjunction with intraoperative exploration, led to suspicion of gastric cancer. The gastric wall was cut open to retrieve the tumor, which was subjected to snap freezing and laboratory examination. The results indicated gastric adenocarcinoma. Therefore, the patient received an intraoperative diagnosis of obstructive jaundice, hilar cholangiocarcinoma, and gastric cancer.

The patient's family members or trustees were informed of the intraoperative findings, the details of the possible adverse prognosis, and the advantages and disadvantages of different surgical approaches before they signed the informed consent. The patient underwent resection of hilar cholangiocarcinoma (Roux-en-Y choledochojejunostomy) + radical resection of proximal gastric cancer (end-to-side esophagogastric anastomosis). The operation lasted for 5.5 hours, resulting in a total blood loss of approximately 600 mL, and transfusion was not performed. The surgical specimens are shown in Fig. 2.

Postoperative pathological examination of the gastric lesion (Fig. 3) revealed the following results: ulcerative, moderately differentiated gastric adenocarcinoma; intestinal type in the Lauren classification of stomach cancer; an approximate tumor size of 4.5 cm × 3 cm; invasion into the adventitia and lower esophagus; presence of nerve infiltration; lack of intravascular tumor embolus; clean surgical margins and anastomotic openings; no tumor in the lymph nodes of the lesser curvature of the stomach (0/7); and no tumor in the greater and lesser omental tissues. Immunohistochemistry of the gastric lesion showed the following results: cytokeratin 7 (CK7) (+), CK20 (–), caudal type homeobox 2 (CDx-2) (–), Villin (+), synaptophysin (Syn) (–), chromogranin (CgA) (–), neuron specific enolase (NSE) (–),

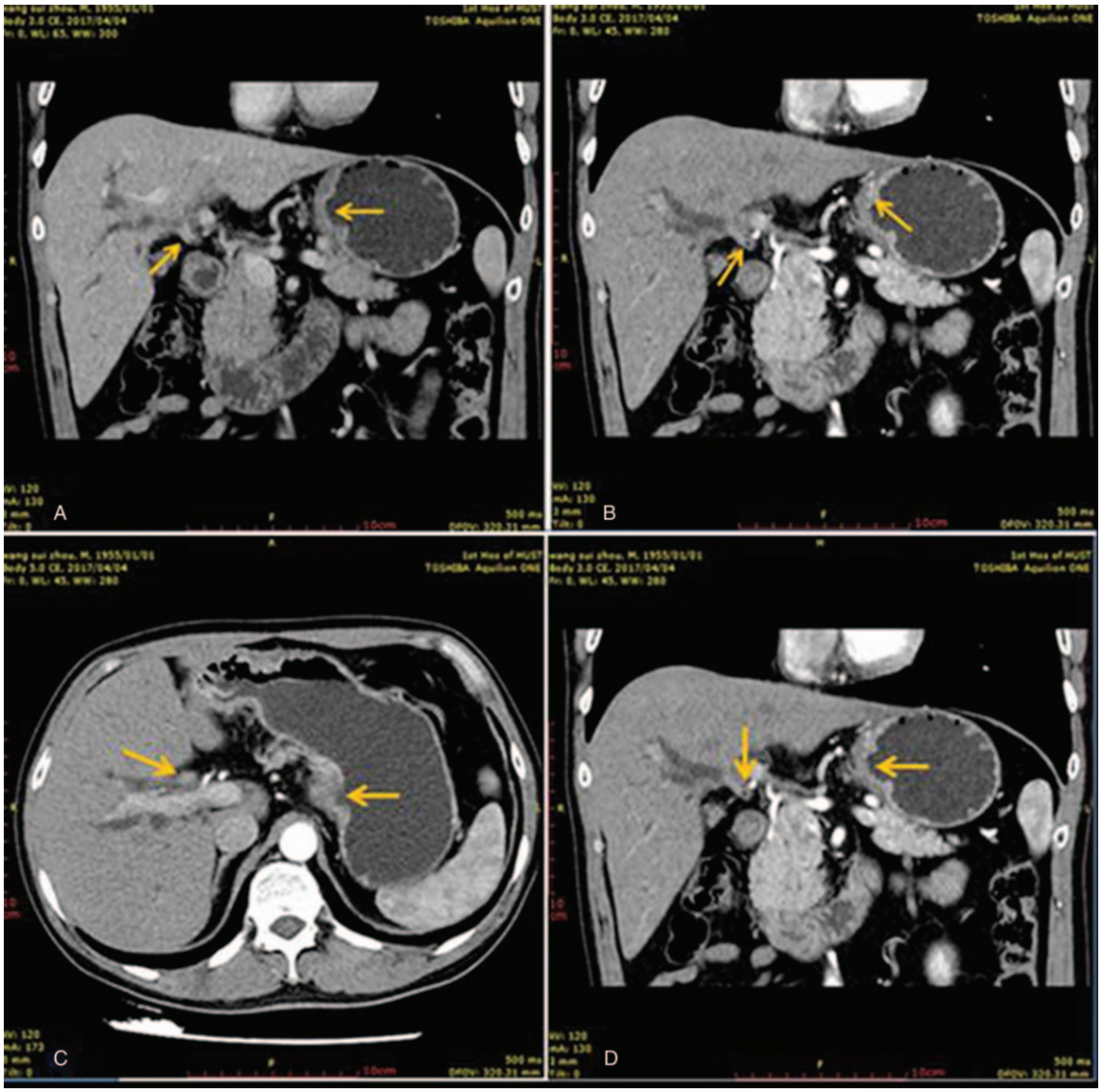

Figure 1. Pretreatment abdominal contrast-enhanced computed tomography images. A and B: Dilation of the hilar bile duct in arterial phase, a hilar soft tissue mass of 12 mm × 0.5 mm with obviously enhanced, irregular thickening of the stomach wall in the lesser curvature. C and D: A soft tissue mass was seen at the confluence of the right and left hepatic ducts in the portal phase, and the stomach wall was irregularly thickened. The soft tissue mass at the confluence of the right and left hepatic ducts and the irregular thickening of the stomach wall were obviously strengthened in arterial phase.

cluster of differentiation 56 (CD56) (–), 10% Ki67 (+), broad-spectrum CK (+), CK19 (+), and human epidermal growth factor receptor-2 (HER-2) (0). In addition, differentiated adenocarcinoma of the bile duct invaded into the entire wall of the bile duct and the surrounding liver tissue. The surgical margin of the common bile duct was clean. No tumor was identified in the gallbladder. Immunohistochemistry of the cholangiocarcinoma revealed the following results: CK8 (+), CK7 (+), CK20 (–), Villin (+), CK19 (+), HER-2 (0), and CDx-2 (–).

After the operation, the patient experienced good overall recovery despite developing a mild biliary fistula. Twelve days after the operation, the patient maintained the abdominal drainage tube and was discharged. Thirty days after the operation, the patient attended an outpatient follow-up visit in which he underwent abdominal color ultrasonography and was found to have no ascites; therefore, the drainage tube was removed. Due to personal reasons, the patient did not follow the physician's advice to receive standardized therapy. Instead, he received unconventional chemotherapy with oral tegafur and enjoyed good survival conditions until October 5, 2017. A CT scan revealed no apparent signs of metastasis. Both the physicians and the patient were satisfied with the therapeutic outcome. On January 2, 2018, the patient developed anorexia and wasting and received an outpatient review in which he was found to exhibit multiple metastases in the abdominal cavity. Unfortunately, he refused the physician's advice and rejected therapy. In February 2018, the patient died.

3. Discussion

According to the available literature, the incidence of MPM is generally between 0.7% and 11.7%, but in recent years, a

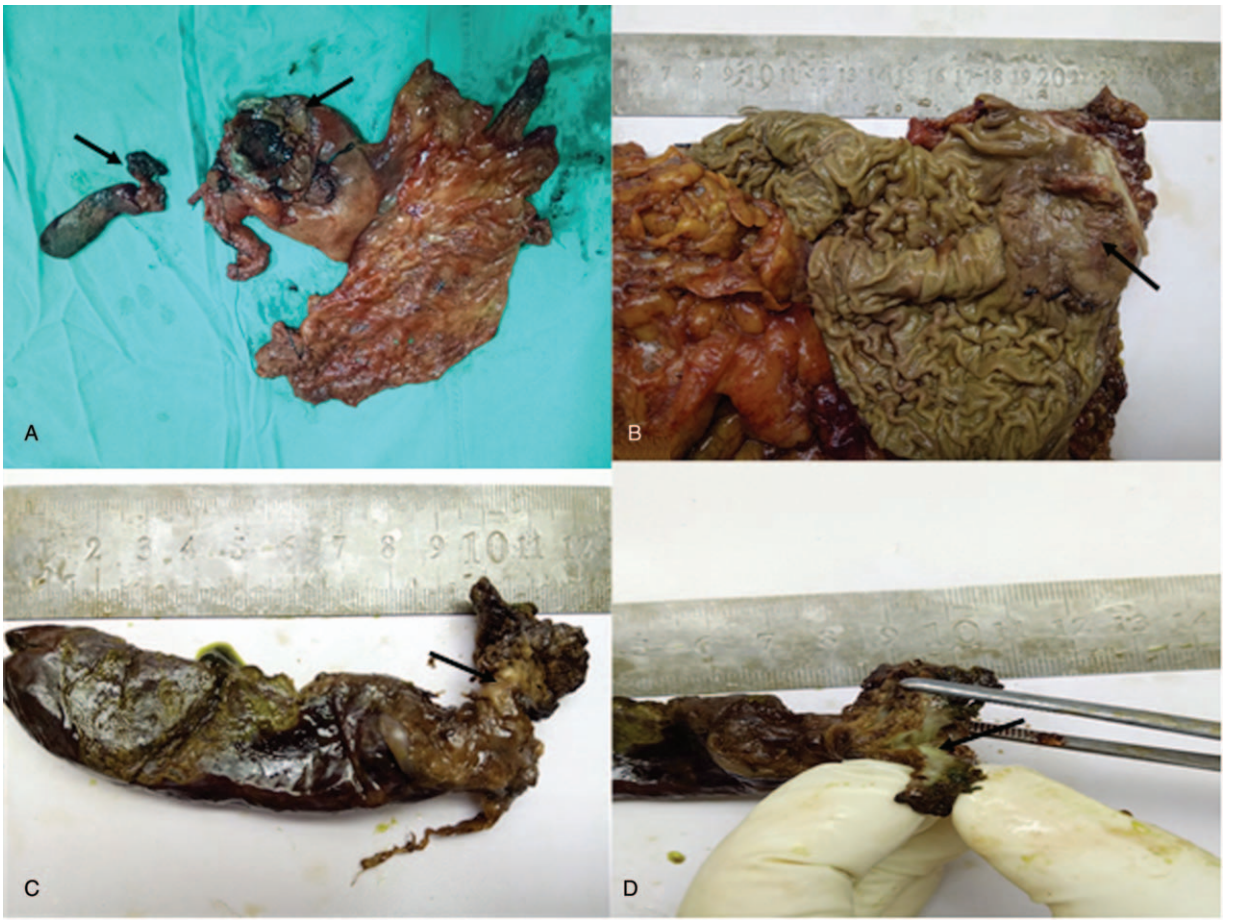

Figure 2. A: Surgical specimens of the cholangiocarcinoma and gastric adenocarcinoma. B: Gross specimen of gastric adenocarcinoma. C and D: Gallbladder and biliary tumor tissue.

gradual increase has been observed,[4,8,9] which may be related to the aging population and advancements in medical equipment and technology.[10,11] Between 1973 and 2000, as many as 10% of cancer survivors in the United States were reportedly diagnosed with at least 1 additional type of primary cancer, and this incidence has been increasing in recent years.[12] Regarding the number of primary malignant tumors, MPM with 2 types of primary malignant tumors is relatively common, whereas MPM with ≥3 types of primary malignant tumors is rare.[8,13]

The pathogenesis of MPM remains unclear, but several risk factors of the disease have been identified, including hereditary elements, immune deficiency and immune escape of cancer cells, accumulation of genetic mutations and abnormal gene expression, and administration of radiotherapy, chemotherapy, and some drugs.[14,15] In the process of human aging, weakening immune function leads to a decreased surveillance capacity of immune cells to detect tumor cells, causing a shift of the internal environment to be more conducive to the growth and proliferation of tumor cells. Therefore, as people become older and live longer, they are more vulnerable to carcinogens, resulting in an increased occurrence of precancerous lesions. In addition, precancerous lesions are highly likely to progress to malignancies due to accumulation of genetic changes. These factors collectively contribute to an increased incidence of MPM.

The patient was admitted to this hospital mainly because of anorexia and progressive aggravation of jaundice. Subsequent examination showed a significant increase in CA199 and a normal CEA level but identified no classical symptoms of gastric cardiac cancer, such as dietary choking, acid regurgitation, heartburn, or abdominal pain. Therefore, the patient was mainly treated for obstructive jaundice because during the preoperative examination of the CT data, the imaging experts and clinicians focused mostly on the classification, location, and size of the obstruction, hilar lymph nodes, and other aspects pertinent to cholangiocarcinoma and overlooked the gastric lesion. Thus, the patient was not preoperatively diagnosed with gastric cancer.

This particular case reminds clinicians and imaging experts that a patient's condition must be assessed comprehensively, objectively, and systematically. Because the diagnostic rate of MPM is related to a surgeon's clinical experience and relevant medical knowledge (including awareness of the likelihood of MPM), prevalence is inadequate for explaining the multiple clinical manifestations of a single disease. Instead, a scientific mode of thinking based on clinical experience should be established to increase vigilance and therefore avoid a correct diagnosis being masked by some ostensibly "obvious and reasonable" conclusions, thus minimizing misdiagnosis. Because patients with primary tumors have a markedly increased risk of developing other secondary malignancies,[8,16] considerable

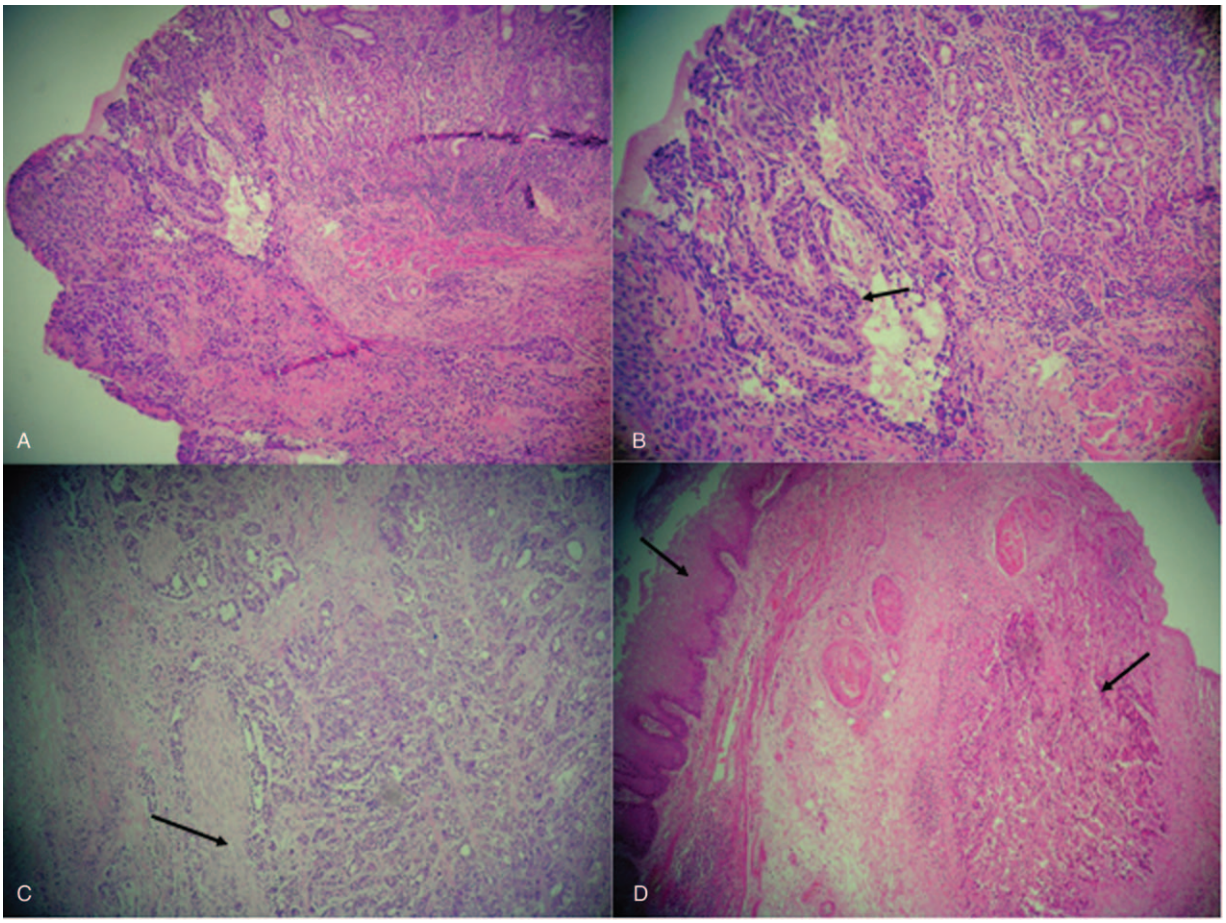

Figure 3. Histopathological findings (hematoxylin and eosin staining). A: Gastric adenocarcinoma tissue (magnification ×40). B: Gastric adenocarcinoma tissue (magnification ×100). C: Perineural invasion in gastric adenocarcinoma (the arrow points to the nervous tissue, magnification ×100). D: Gastric adenocarcinoma invading the esophagus (the left arrow points to the esophageal squamous epithelium, and the right arrow points to the gastric cancer cell, magnification ×100).

attention should be directed toward their postoperative follow-up visits, where tumor recurrence or the occurrence of other types of primary tumors can be promptly discovered.

Given that no reports of similar cases are available, we identified the following lessons from this clinical case. First, during conventional laparotomy or laparoscopic surgery, exploration of the abdominal organs must be carefully executed in accordance with standard procedures. Taking this patient an example, if exploratory laparotomy had not been rigorously and meticulously performed, then the crucial diagnosis of gastric cancer may have been easily overlooked. Accordingly, the patient would have required another operation or could have suffered adverse consequences related to survival.

Since the patient was intraoperatively diagnosed with proximal gastric cancer and hilar cholangiocarcinoma, we communicated with his family members and recommended the following treatment options: radical total gastrectomy + radical resection of hilar cholangiocarcinoma (left hemihepatectomy); and an alternative of palliative treatment. The trustee of the patient refused the plan due to concern regarding the patient's poor tolerance of large operations. Correspondingly, the patient underwent resection of hilar cholangiocarcinoma (Roux-en-Y cholangiojejunostomy) + radical resection of proximal gastric cancer (end-to-side esophagogastric anastomosis). After the operation, the patient was advised to undergo precision chemotherapy or palliative chemotherapy with 5-fluorouracil drugs, which was determined according to the results of his molecular diagnosis of cancer. Unfortunately, the patient refused these standardized therapies for his own reasons. A study on psychological distress and health behaviors among patients with MPM[17] revealed that compared with single-cancer survivors, MPM survivors experienced significantly higher psychological distress and relevant mental risks; however, interventions can be provided to ameliorate distress, reduce negative health effects, and improve compliance. The patient in this study had poor compliance, possibly due to his economic situation, psychological factors, and the current medical environment in China. Consequently, his clinicians could not strictly follow the relevant clinical guidelines to perform standardized operations and provide comprehensive treatment. This result is consistent with the unfavorable medical challenges facing Chinese physicians reported in a Lancet article, which described poor medical markets, a poor clinical environment, and poor doctor–patient relationships.[18]

MPM is characterized by a poor prognosis,[4] with a 5-year survival rate after hilar cholangiocarcinoma resection of only 25% to 50%.[19,20] Local recurrence and metastasis are the main factors affecting survival.[21] Of note, the patient did not receive

standardized postoperative therapy. Although he lived and worked normally for 8 months after the operation, he died 10 months after surgery.

In summary, the morbidity and mortality of MPM are expected to increase further as humans experience increases in both the cancer incidence and life expectancy. This paper reports a case of synchronous MPM comprising cholangiocarcinoma and gastric adenocarcinoma for the first time. This report reminds us to pay close attention to the likelihood of MPM in the future. To this end, physicians and imaging clinicians should explore all clinical possibilities. Intraoperative exploration can significantly help diagnose cases of MPM. Furthermore, standardized postoperative adjuvant therapy may extend patients' disease-free survival time and total survival time.

Author contributions

Conceptualization: Jun-Jun Sun.
Data curation: Yan-Hui Yang, Qing Deng, Tian-Bao Yang, Qian Deng.
Funding acquisition: Jiang-Bo Liu.
Writing – original draft: Yan-Hui Yang, Tian-Bao Yang.
Writing – review & editing: Yan-Hui Yang, Yang Gui, Yuxiang Zhang, Wei-Feng Liu, Jun-Jun Sun.

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