Case Report

Spontaneous Hepatic Infarction in a Patient with Gallbladder Cancer

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Abstract

Hepatic infarction is known as a rare disease entity in nontransplant patients. Although a few cases of hepatic infarction have been reported to be linked with invasive procedures, trauma, and hypercoagulability, a case of spontaneous hepatic infarction in a nontransplanted patient has hardly ever been reported. However, many clinical situations of patients with cancer, in particular biliary cancer, can predispose nontransplant patients to hepatic infarction. Besides, the clinical outcome of hepatic infarction in patients with cancer can be worse than in patients with other etiologies. As for treatment, anticoagulation treatment is usually recommended. However, because of its multifactorial etiology and combined complications, treatment of hepatic infarction is difficult and not simple. Herein, we report a case of fatal hepatic infarction that occurred spontaneously during the course of treatment in a patient with gallbladder cancer. Hepatic infarction should be considered as a possible fatal complication in patients during treatment of biliary malignancies.

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Introduction

Hepatic infarction is a very rare disease entity and usually occurs in patients who underwent liver transplantation. Although a few cases of hepatic infarction with various etiolo-

gies and clinical outcomes have been reported in nontransplanted patients, most of those cases resulted from iatrogenic causes such as operations or invasive procedures. Therefore, having a suspicion of hepatic infarction in a nontransplanted patient who did not undergo any invasive procedure is difficult. In particular, in case of patients with hepatobiliary malignancy, right upper quadrant pain – which is one of the common symptoms of hepatic infarction – can be confused with cancer pain. However, malignancy, especially biliary malignancy, can cause various factors predisposing to hepatic infarction with regard to the disease itself or the treatment received. Herein, we report a case of spontaneous hepatic infarction that occurred during the course of treatment in a patient with gallbladder cancer.

Case Report

A 60-year-old female patient was admitted to the emergency department for cough, fever, and poor oral intake on February 15, 2016. As assessed by her past history, she had undergone extended right hemihepatectomy with hepaticojejunostomy for locally advanced gallbladder cancer which closely abutted on the right hepatic artery on December 3, 2014. Subsequently, she received adjuvant 5-fluorouracil-based concurrent chemoradiation therapy. During a regular follow-up, a recurrent mass which extended from the hepaticojejunostomy site to the superior mesenteric artery was identified. Therefore, she received palliative systemic chemotherapy with a regimen of gemcitabine (1 g/m² on day 1, day 8 q 21 days) plus cisplatin (25 mg/m² on day 1, day 8 q 21 days). After 2 cycles of chemotherapy, her disease progressed. Thus, the chemotherapy regimen was changed to capecitabine (2,000 mg/m² on day 1 to day 14 q 21 days) plus cisplatin (60 mg/m² on day 1 q 21 days).

Ten days after the 2nd cycle of the changed regimen, she presented to our emergency department with the abovementioned symptoms, and multifocal pneumonia was identified on the initial chest X-ray. On initial laboratory examination, an elevation of C-reactive protein (262 mg/l) and a mild elevation of liver enzyme levels (AST: 130 U/l; ALT: 241 U/l) were identified. No other specific abnormalities were found. Therefore, we prescribed intravenous antibiotics (cefoperazone/sulbactam 4 g/day) for pneumonia and performed supportive treatment including intravenous fluid infusion. Her symptoms were relieved after initial treatment. However, 1 day after admission, she complained of sudden right upper quadrant pain with tenderness. In addition, systemic hypotension (70/50 mm Hg) and metabolic acidosis (pH 7.43, pCO₂ 15.9 mm Hg, pO₂ 83.2 mm Hg, and HCO₃ 10.4 mmol/l) were revealed. We immediately performed abdominal CT scanning with contrast and identified extensively distributed, peripheral, wedge-shaped low attenuation areas within the remaining liver parenchyma, which is consistent with hepatic infarction (fig. 1a, b). Along with this finding, thrombosis filling the portal vein was identified, and the left hepatic artery was invisible (fig. 1d). A progressing mass encasing the common hepatic artery as well as thrombosis inside the lumen of the common hepatic artery was also revealed (fig. 1f). These findings had not previously been observed on abdominal CT (fig. 1c, e). Although we did not perform an underlying hypercoagulability workup including protein C, protein S, and antithrombin III levels, her coagulation profiles were within the normal range at the time of the diagnosis of gallbladder cancer. She did not have any history of arrhythmia, and echocardiography did not detect any thrombus in the cardiac chamber. One day after the event, the liver enzyme levels were elevated abruptly (AST 3,042 U/l; ALT 1,755 U/l) and hematochezia was suddenly noticed. Due to the combined severe thrombocytopenia, prolonged prothrombin time/activated partial thrombin time, and hematochezia, we could not perform

anticoagulation therapy. Therefore, she received only supportive treatment with intravenous fluid, inotropics, antibiotics, and transfusion. Although the liver enzyme levels showed improvement 3 days after the episode (fig. 2), bilirubin and creatinine levels were still elevated. On the 4th day, she became lethargic and her urine output decreased dramatically. We performed continuous renal replacement therapy with further possible supportive treatment. However, she eventually died of sudden cardiac arrest accompanied by seizure, which might have been caused by metabolic encephalopathy.

Discussion

Spontaneous hepatic infarction is known to be very rare due to the unique dual hepatic blood supply from the hepatic artery and the portal vein, although it occasionally occurs in patients who underwent liver transplantation. However, special occasions with combined multiple risk factors or iatrogenic causes can predispose nontransplanted patients to this rare disease entity. Based on previous reports, trauma, underlying hypercoagulability, atherosclerosis, use of splanchnic vasoconstrictor agents, pancreatitis, previous vascular intervention including transcatheter arterial embolization or intra-arterial chemoinfusion for hepatocellular carcinoma, hepatic artery pseudo-aneurysm after an invasive hepatic procedure, and systemic hypotension have been presented as possible causes of hepatic infarction [1–6]. Although other malignancies except hepatocellular carcinoma have not been presented as a risk factor for hepatic infarction, theoretically they, especially biliary malignancies, can be a predisposing factor in some respects. Firstly, hepatic artery reconstruction, manipulation, or inadvertent injury during surgery for biliary malignancy can be a risk factor for postoperative vascular complications including thrombosis [7, 8]. Secondly, direct invasion of the hepatic artery or portal vein by adjacent tumor can compromise the patency of hepatic blood flow. Thirdly, anticancer treatment such as radiation therapy and chemotherapy can induce vascular damage resulting in thrombosis. Lastly, the malignancy itself can be a cause of hypercoagulable state. An association of portal vein thrombosis with biliary malignancy has been reported before. Based on one retrospective study by Jeon et al. [9], the overall risk of venous thromboembolism in 273 cholangiocarcinoma patients was 11.4%, and portal vein thrombosis accounted for a substantial part. Furthermore, the authors insisted that progression of stage, a high level of C-reactive protein, and treatment with chemotherapy were strongly associated with the occurrence of thromboembolism. Among chemotherapeutic agents, fluoropyrimidine was strongly associated with thromboembolism.

Our patient also had multiple risk factors at diagnosis of the hepatic infarct. Specifically, her previous radiation treatment, systemic hypotension induced by dehydration and infection, as well as direct obliteration of the hepatic vessels by the progressed tumor possibly contributed to the occurrence of the massive hepatic infarction. Moreover, the diminished remnant liver, due to a previous right hemihepatectomy, might have attenuated its compensatory capacity.

As for treatment, immediate anticoagulation therapy has been recommended for portal vein thrombosis [10]. In one prospective study, the recanalization rate of the portal vein after anticoagulation therapy was 39% [11]. However, the effectiveness of anticoagulation therapy in patients with malignancy is uncertain, and if concomitant coagulation abnormalities due to hepatic dysfunction exist, the safety and feasibility of anticoagulation therapy could not be ensured. Intestinal infarction, which can be complicated by acute portal vein thrombosis, also interrupts anticoagulation treatment due to concern of intestinal bleeding

[12]. As an interventional approach, intra-arterial stenting or percutaneous angioplasty can be helpful for hepatic artery complications (thrombosis, stenosis) in liver-transplanted patients. However, the effectiveness of vascular intervention in nontransplanted patients is not certain either [13, 14]. Consequently, in case of hepatic infarction, which usually includes both hepatic artery occlusion and portal vein thrombosis, treatment is more complicated and difficult. Occasionally, conservative treatment can be considered for patients with segmental or subsegmental infarctions. In our case, although we confirmed the hepatic infarct shortly after the appearance of symptoms, we could not try an anticoagulation or interventional approach because of multifocal lesions and the poor condition of the patient. She eventually expired even though her liver enzyme levels had decreased 3 days after the episode. Many other previous reports also showed a poor outcome irrespective of anticoagulation treatment [15, 16].

The point that is worth considering is whether early recognition or suspicion of hepatic arterial insufficiency based on clinical symptoms might have been possible before the fatal hepatic artery thrombosis occurred. Our patient occasionally complained of vague right upper quadrant and epigastric pain and unexplainable mild elevation of liver enzyme levels throughout the follow-up period. However, it was not certain that the elevated liver enzyme levels were caused by liver damage from chronic vascular insufficiency, and the symptom was so-called liver angina. Therefore, if it is not possible to discriminate patients who need empirical or prophylactic anticoagulation treatment, giving careful attention to apprehending risk factors for hepatic infarct and avoiding evitable risk factors in vulnerable patients like our case is rather reasonable.

Conclusion

We presented a rare case of spontaneous hepatic infarction which occurred during the course of treatment in a patient with cancer. Because hepatic infarction could be fatal in patients with biliary malignancy, caution about evitable predisposing factors such as dehydration or systemic hypotension from infectious episodes is required. We call the attention of physicians who treat patients with biliary malignancies to this rare case.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors state that they have no conflict of interest.

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Fig. 1. **a, b** Abdominal contrast-enhanced CT showing multiple peripheral wedge-shaped hypodense areas. **c** Abdominal contrast-enhanced CT which had been performed 3 months before the hepatic infarct, showing the well-identified left hepatic artery (arrows). **d** At diagnosis of the hepatic infarct, abdominal contrast-enhanced CT showed a thrombus in the portal vein, and the hepatic artery could not be identified (arrow). **e** Abdominal contrast-enhanced CT which had been performed 3 months before the hepatic infarct, showing the well-identified common hepatic artery (arrow). **f** At diagnosis of the hepatic infarct, a thrombus in the common hepatic artery was identified (arrow).

Fig. 2. Trend of liver enzyme (in U/l; **a**) and bilirubin (in mg/dl; **b**) levels during the hospital stay.