American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2021; 22: e929493
DOI: 10.12659/AJCR.929493

Received: 2020.10.28
Accepted: 2020.12.23
Available online: 2021.01.07
Published: 2021.02.18

Ramucirumab-Induced Hepatocellular Carcinoma Rupture and Gastrointestinal Perforation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 66-year-old
Final Diagnosis: Gastrointestinal perforation • hepatocellular carcinoma
Symptoms: Altered mental state
Medication: —
Clinical Procedure: Exploratory laparotomy
Specialty: Critical Care Medicine • Gastroenterology and Hepatology • Oncology

Objective: Rare disease

Background: Hepatocellular carcinoma (HCC) is a primary liver malignant tumor that typically but not always develops in the setting of chronic liver disease, particularly in patients with cirrhosis or chronic hepatitis B virus infection. Advanced HCC portends a poor prognosis; however, recent advances in first-line and second-line treatment options yield significant survival improvements. Ruptured HCC is an uncommon presentation that occurs in approximately 3-26% of patients.

Case Report: We present a case of a patient with HCC who was undergoing treatment with the antiangiogenic monoclonal antibody ramucirumab. Subsequently, he presented with signs and symptoms of acute abdomen. The abdominal imaging revealed pneumoperitoneum with multiple abdominal and pelvic collections. The patient underwent exploratory laparotomy and was found to have necrotic liver parenchyma, which appeared to be perforated. Also, a microperforation was noted in the proximal duodenum. The pathology report from liver specimens showed fragments of hepatocellular cancer with extensive necrosis.

Conclusions: The mechanism of tumor rupture in HCC is poorly understood. The so-called vascular injury hypothesis states that collagen expansion and elastin proliferation in the arterial wall supplying the tumor could be the leading cause of HCC rupture. We believe that the process mentioned above was accelerated in our patient using the antiangiogenic factor ramucirumab. A similar antiangiogenic mechanism is also implicated in gastrointestinal hemorrhage and perforation related to this drug.

Keywords: Antineoplastic Agents • Carcinoma, Hepatocellular • Pneumoperitoneum

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/929493

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Background

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related mortality worldwide, with over 780,000 deaths in 2018. With a 5-year survival of 18%, liver cancer is the second most lethal tumor after pancreatic cancer [1]. Ramucirumab is a recombinant human immunoglobulin G1 monoclonal antibody that binds to the extracellular binding domain of vascular endothelial growth factor receptor 2 (VEGFR-2) and prevents the binding of VEGFR ligands, thus inhibiting the angiogenesis pathways involved in the development and progression of cancer [2]. It is one of the treatment modalities in treating HCC and is known to be associated with hypertension, proteinuria, hemorrhage, and gastrointestinal (GI) perforation. We present a rare case where ramucirumab was associated with tumor rupture in a known case of HCC and duodenal perforation.

Case Report

We report a case of a 66-year-old man with medical comorbidities of stage 3b HCC, liver cirrhosis, chronic hepatitis C (Child-Turcotte-Pugh B), and hypothyroidism who presented to the emergency department with worsening altered mental status. The patient was diagnosed with HCC 2 years before the presentation. The mass was 3 cm in size and was located in segments V and VI in the right lobe of the liver (**Figure 1**). He was initially started on treatment with pembrolizumab and Lenvatinib (as part of study treatment). Later on, because of treatment failure, therapy was changed to ramucirumab, an approved second-line treatment in the management of HCC. Four months after starting ramucirumab, he presented to our hospital. His initial vital signs showed blood pressure of 145/90 mmHg, pulse of 92 beats/min, respiratory rate of 17 breaths/min, and oxygen saturation of 98% on room air. Physical examination showed no focal neurological deficits, widespread abdominal tenderness, and absent bowel sounds. Laboratory parameters were as follows: hemoglobin 11.8 g/dL, leukocytes 14×10/μL, alanine aminotransferase 17 U/L, aspartate aminotransferase 54 U/L, total bilirubin 2.0 mg/dL, direct bilirubin 1.0 mg/dL, ammonia 91 μmol/L, and lactate 4.7 mmol/L. The other parameters were within the normal range. His baseline liver function tests (1 month before presentation) were as follows: alanine aminotransferase 15 U/L, aspartate aminotransferase 50 U/L, total bilirubin 1.7 mg/dl, international normalized ratio 1.6, and albumin 2.8 g/L. Computed tomography (CT) of the head and chest X-ray were negative for any significant acute pathology. CT of the abdomen and pelvis with contrast material revealed pneumoperitoneum with multiple abdominal and pelvic collections (**Figure 2**).

In the setting of leukocytosis, lactic acidosis, peritoneal signs on physical examination, and CT scan with multiple fluid collection

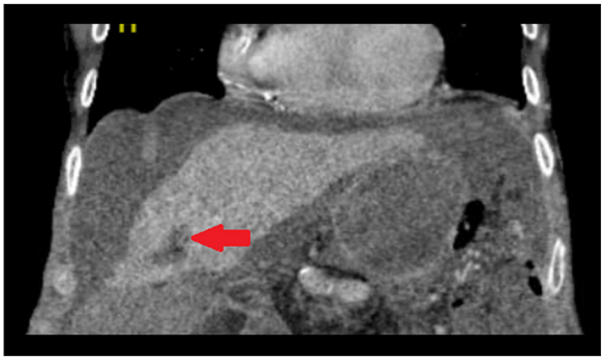

Figure 1. Computerized tomography scan of abdomen and pelvis showing the tumor in the right lobe of the liver.

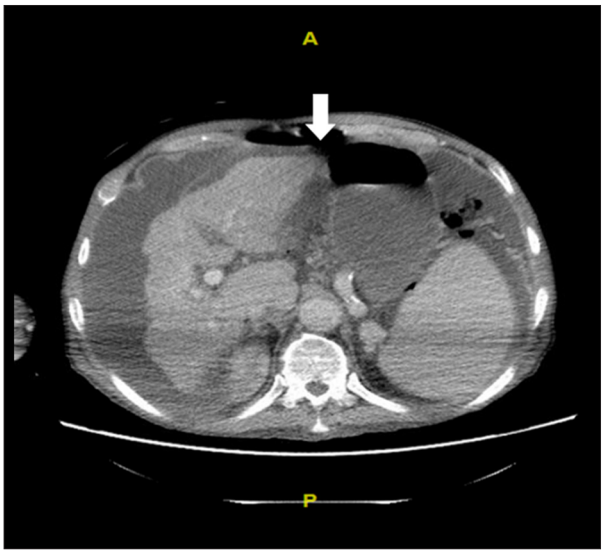

Figure 2. Computerized tomography scan of abdomen and pelvis with contrast material consistent with pneumoperitoneum and cirrhotic liver.

areas, the initial impression was suspected gastric or duodenal perforation. The patient was started on broad-spectrum antibiotics and underwent exploratory laparotomy and was found to have a nodular shrunken liver with necrotic parenchyma in segments V and VI of the liver, which appeared to be perforated. Also, a microperforation was noted in the proximal duodenum. Necrotic tissue was removed, the omentum was packed in the liver bed, and 6 L of ascitic fluid was drained. The pathology sample (taken from necrotic liver tissue) showed fragments of hepatocellular carcinoma with extensive necrosis (**Figure 3**). The peritoneal fluid analysis was consistent with secondary bacterial peritonitis (white blood cell count of 6200 cells/mm^3 with 92% neutrophils), and cytology was negative for malignant cells.

Despite antibiotic therapy with piperacillin-tazobactam, the patient developed multiorgan dysfunction. Therefore, we implemented a palliative therapy approach, and the patient was discharged to hospice care.

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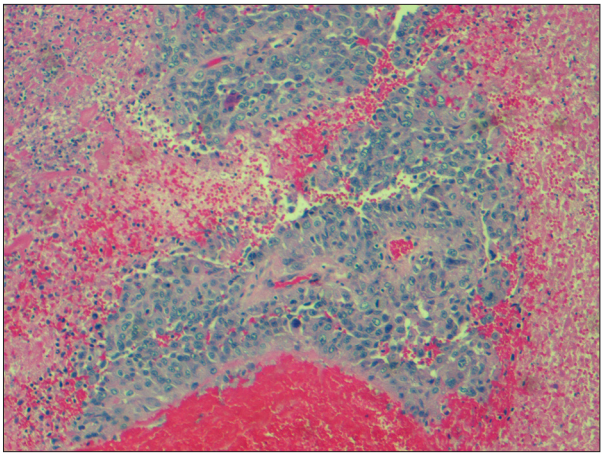

Figure 3. Histopathology showing a nest of tumor cells invading the liver parenchyma (hematoxylin and eosin stain, magnification ×40).

Discussion

In 85-95% of cases, HCC develops in patients with cirrhotic liver. Studies have shown that once cirrhosis has developed, HCC will occur at a rate of 2-7% per year [3]. The incidence/mortality ratio in HCC is almost 1: 1, which shows that most of the patients with HCC ultimately die [4]. The incidence of spontaneous rupture is <3% in western countries. The overall mortality is almost 50% in Asian countries, with an incidence of 12-14% [5]. Ramucirumab is a recombinant monoclonal antibody that inhibits VEGFR-2. There is an increasing amount of evidence that this antiangiogenic drug is associated with an increased risk of hemorrhage and GI perforation, which may be severe or sometimes fatal. A meta-analysis study published in 2016 including 4963 patients with a variety of solid tumors from 11 different studies demonstrated that overall incidences of all-grade and high-grade hemorrhagic events in cancer patients were 27.6% and 2.3%, respectively [6]. The incidence of all-grade GI perforation with ramucirumab was 1.5%, with 29.8% mortality in another study [7]. Another case report of gastric cancer treated with ramucirumab was complicated by small intestinal metastasis and, ultimately, perforation [8].

Spontaneous rupture is the third leading cause of mortality in the patients with HCC after carcinoma progression and liver failure [9]. In a study, Zhu et al concluded that the presence of liver cirrhosis, hypertension, tumor size >5 cm, and extrahepatic invasion increase the risk of spontaneous rupture [10]. The mechanism of tumor rupture in HCC is poorly understood. The VEGF signaling pathway is broadly involved in HCC angiogenesis and lymphangiogenesis and seems to play a crucial role in disease pathogenesis [11]. The so-called vascular injury hypothesis states that certain changes in the arterial walls supplying the tumor could lead to HCC rupture. These vascular changes may include collagenase expansion leading to degradation of type IV collagen and elastin proliferation [9,12]. We believe that the process mentioned above was accelerated in our patient using the antiangiogenic factor ramucirumab (an inhibitor of VEGF). It is difficult to prove this association; therefore, large-scale studies are needed to explore this association. Also, spontaneous rupture is more common in tumors of size >5 cm. Although possible, it is rare to see a spontaneous rupture in a tumor <5 cm in size. Because of its antiangiogenic activity, there is a concern for serious antiangiogenic adverse effects, including impaired wound healing, GI perforations, and hemorrhage. The gross specimen recovered from surgery in our patient showed necrotic liver tissue with clots, whereas the biopsy specimen showed HCC with extensive necrosis.

Another important finding in our patient was the presence of a microperforation in the proximal duodenum leading to pneumoperitoneum. To our knowledge, this patient had no known risk factors (eg, alcohol abuse, trauma, foreign body ingestion, peptic ulcer disease, primary or metastatic intestinal tumor, nonsteroidal anti-inflammatory drug abuse) for GI perforation. A study done by Wang et al concluded that ramucirumab was associated with GI perforation, with a relative risk of 2.56 [13]. In another study, the incidence rate of all-grade GI perforation with ramucirumab was 1.5%, with a mortality rate of 29.8% [7]. The Food and Drug Administration recommends discontinuing ramucirumab permanently in patients who experience GI perforation. Although unclear, the proposed mechanism for GI perforation is similar to that for HCC rupture (antiangiogenesis) [8].

The best treatment for a ruptured HCC is still debated, the primary goal being the correction of hypovolemic shock. The mortality rate is 85-100% in patients who are managed conservatively [9]. Therapeutic options must be individualized after the initial resuscitation on the basis of tumor staging and resection feasibility. Transarterial embolization effectively controls bleeding from ruptured HCC in the acute phase, with serum bilirubin levels, shock on hospital admission, and prerupture disease state being the critical prognostic factors. Elective liver resection after achieving initial hemostasis via transarterial embolization is preferred over emergency liver resection because, in later cases, the tumor stage and liver function reserve are unclear [14].

Conclusions

Ramucirumab is a new immunotherapy that has been found to be effective in advanced HCC treatment, but there is a concern for serious antiangiogenic adverse effects, including impaired wound healing, GI perforations, and hemorrhage. We presented a rare case of HCC rupture and GI perforation in a patient undergoing treatment with ramucirumab.

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