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The primary aim of *World Journal of Gastrointestinal Surgery* (WJGS, *World J Gastrointest Surg*) is to provide scholars and readers from various fields of gastrointestinal surgery with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGS mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal surgery and covering a wide range of topics including biliary tract surgical procedures, biliopancreatic diversion, colectomy, esophagectomy, esophagostomy, pancreas transplantation, and pancreatectomy, etc.

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Massive bleeding from a gastric artery pseudoaneurysm in hepatocellular carcinoma treated with atezolizumab plus bevacizumab: A case report

Fu-Wen Pang, Bin Chen, De-Ti Peng, Jian He, Wei-Cheng Zhao, Tuan-Tuan Chen, Zong-Gui Xie, Hai-Hui Deng

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Abstract

BACKGROUND

The combination of atezolizumab (ATZ) and bevacizumab (BVZ) was approved as first-line systemic therapy for advanced hepatocellular carcinoma (HCC) owing to its superior rates of response and patient survival. However, ATZ + BVZ is associated with increased risk of upper gastrointestinal (GI) bleeding, including arterial bleeding, which is rare and potentially fatal. We present a case of massive upper GI bleeding from a gastric pseudoaneurysm in a patient with advanced HCC who had been treated with ATZ + BVZ.

CASE SUMMARY

A 67-year-old man presented with severe upper GI bleeding after atezolizumab (ATZ) + bevacizumab (BVZ) therapy for HCC. Endoscopy failed to detect the bleeding site. Digital subtraction angiography revealed a gastric artery pseudoaneurysm and contrast extravasation from the inferior splenic artery and a branch of the left gastric artery. Successful hemostasis was achieved with embolization.

CONCLUSION

HCC patients who have been treated with ATZ + BVZ should be followed for 3 to 6 mo to monitor for development of massive GI bleeding. Diagnosis may require angiography. Embolization is an effective treatment.

Key Words: Atezolizumab; Bevacizumab; Hepatocellular carcinoma; Gastric artery pseudoaneurysm; Gastrointestinal bleeding; Case report

Core Tip: Atezolizumab (ATZ) + bevacizumab (BVZ) treatment increases the risk of bleeding in hepatocellular carcinoma (HCC) patients. Gastrointestinal (GI) bleeding is most common and usually arises from esophageal varices. We report a patient with advanced HCC who presented with massive upper GI bleeding from a gastric artery pseudoaneurysm after three cycles of ATZ + BVZ. Gastric artery pseudoaneurysm is rare and often asymptomatic. Mortality is high and emergency endovascular embolization is required. Patients receiving ATZ + BVZ treatment should be followed closely for GI bleeding. Arterial bleeding should be considered when massive GI bleeding occurs. Angiography may be required for diagnosis. Embolization has a role in treatment.

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INTRODUCTION

Primary liver cancer is the fourth leading cause of cancer-related death worldwide[1] and hepatocellular carcinoma (HCC) is the most common type of primary liver cancer[2]. Curative treatment options for early-stage HCC include resection, liver transplantation, and ablation. However, most HCC patients are diagnosed in an advanced stage[2]. In these patients, current guidelines recommend systemic therapy [3].

The multikinase inhibitor sorafenib is an effective first-line systemic agent for treating advanced HCC [4,5]. Lenvatinib, another multikinase inhibitor, is an accepted alternative[6]. Previous studies have shown that both provide modest improvement in survival[6,7]. However, multikinase inhibitors are associated with considerable toxicities which can impair quality of life. The IMbrave 150 trial showed that atezolizumab (ATZ), a programmed cell death ligand 1 antibody and immune checkpoint inhibitor, combined with bevacizumab (BVZ), a vascular endothelial growth factor (VEGF) antibody, achieved a better response rate and rates of progression-free and overall survival than sorafenib in patients with advanced metastatic or unresectable HCC[8]. Based on the trial's results, ATZ + BVZ was approved as first-line systemic therapy for advanced HCC in May 2020. However, compared with sorafenib, ATZ + BVZ was associated with a higher rate of bleeding overall (25.2% *vs* 17.3%) and higher rate of upper gastrointestinal (GI) bleeding (7% *vs* 4.5%). According to previous studies, variceal bleeding accounts for approximately 70% of all upper GI bleeding in HCC patients receiving BVZ or ATZ + BVZ; arterial GI bleeding is rare[9,10]. Here, we report an HCC patient who developed massive GI bleeding from a gastric artery pseudoaneurysm after treatment with ATZ + BVZ.

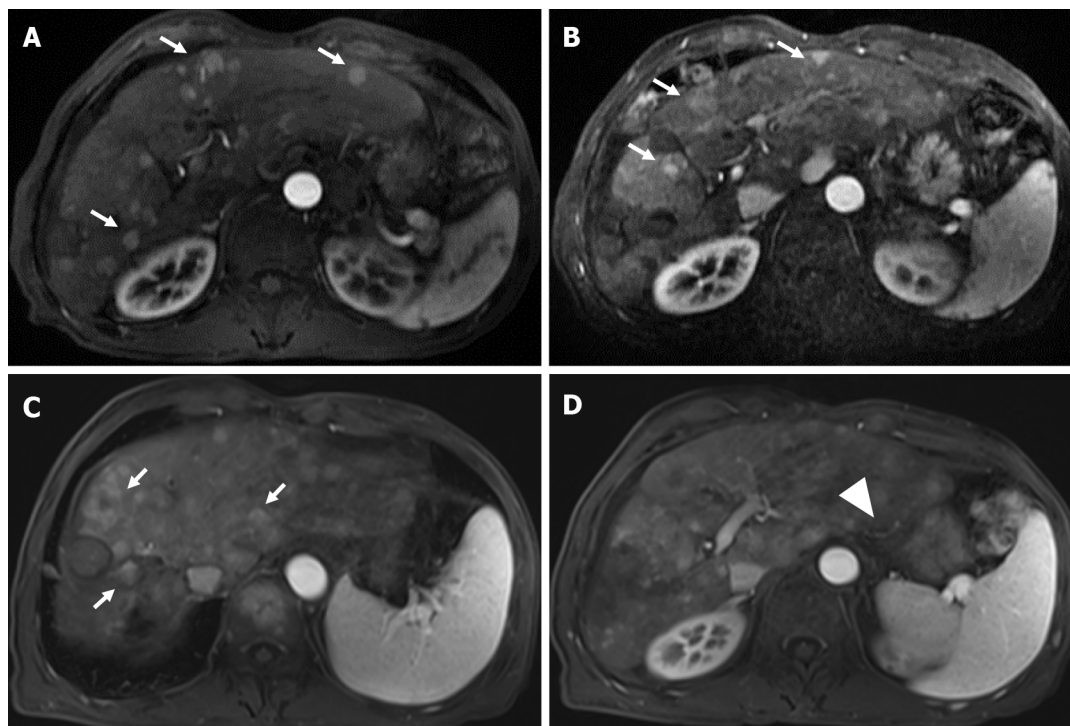
CASE PRESENTATION

Chief complaints

A 67-year-old man with advanced HCC was admitted to our hospital for massive upper GI bleeding after three cycles of ATZ+BVZ treatment.

History of present illness

The patient had been treated with transcatheter arterial chemoembolization (TACE) twice and surgical resection. Owing to HCC progression, he had more recently been treated with sorafenib and four radiofrequency ablation procedures. He was referred to our hospital for evaluation of right upper quadrant abdominal pain in January 2021. Contrast-enhanced abdominal magnetic resonance imaging (MRI) showed multiple enhancing nodules in all segments of the liver (Figure 1A). He underwent TACE twice as well as lenvatinib treatment. Nonetheless, his HCC progressed (Figure 1B). Combination of ATZ (1200 mg) and BVZ (15 mg/kg) every 3 wk was therefore initiated. Blood testing revealed a white blood cell count of $2.83 \times 10^9/L$, hemoglobin concentration of 127 g/L, and platelet count of $149 \times 10^9/L$. Child–Pugh score was 6 (Class A), indicating preserved liver function. Prothrombin time was 2 s longer than normal. Concentrations of the tumor markers des-gamma-carboxyprothrombin and alpha fetoprotein were elevated (29787 mAU/mL and 0.8 ng/mL, respectively). After three cycles, MRI showed continued progression but no remarkable gastroesophageal varices (Figure 1C and D). The



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Figure 1 Pseudoaneurysm bleeding after atezolizumab–bevacizumab treatment. A: Magnetic resonance imaging (MRI) of the abdomen revealed multifocal enhancing hepatocellular carcinoma lesions in the liver (white arrows); B: After transcatheter arterial chemoembolization and lenvatinib treatment, MRI showed disease progression (white arrows); C and D: After three cycles of atezolizumab plus bevacizumab, MRI showed progressive disease (white arrows) but no remarkable gastroesophageal varices (white arrowhead).

patient then underwent another TACE procedure which showed no contrast extravasation in the gastric area (Figure 2). He was discharged without complications. Ten days later, he was admitted to the hospital because of massive hematochezia and melanemesia. The patient's clinical course is shown in Figure 3.

History of past illness

The patient had a history of hepatitis C, cirrhosis, and HCC diagnosed 3 years ago. He also had a remote history of gastric carcinoma treated with partial gastrectomy 30 years previously.

Personal and family history

No specific personal and family history.

Physical examination

On admission, he exhibited signs of hypovolemic shock: Paleness, sweating and low blood pressure (64/38 mmHg).

Laboratory examinations

Hemoglobin concentration and platelet count were 59 g/L and $98 \times 10^9/L$, respectively. Prothrombin time was 5 s longer than normal.

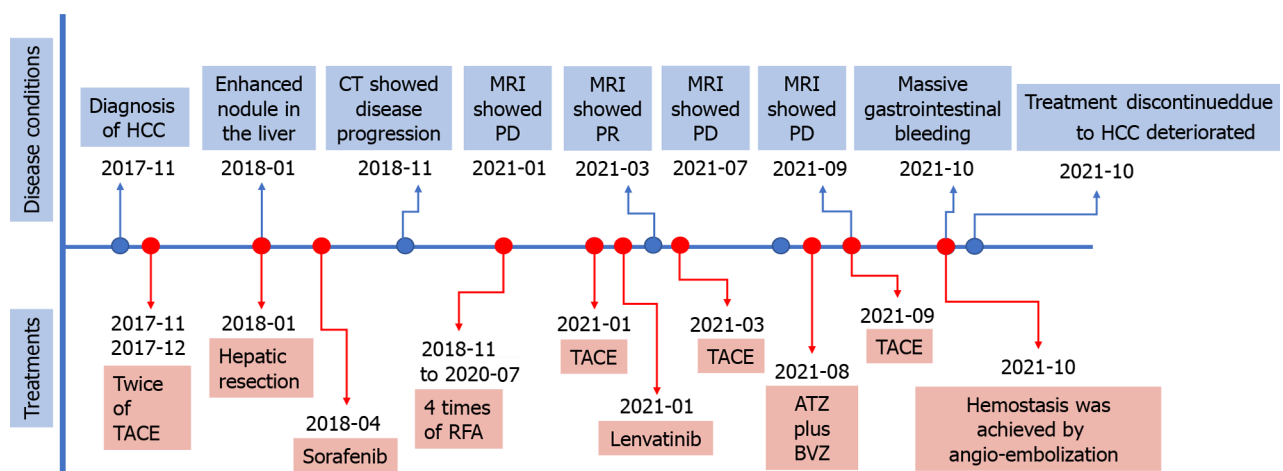
Imaging examinations

His condition did not improve despite infusion of intravenous fluids and a transfusion of packed red blood cells. Because acute upper GI bleeding was suspected, GI endoscopy was performed, which revealed fresh blood and blood clots within the stomach (Figure 4). The blood could not be removed with repeated washings. Esophageal varices and red wale signs were not observed; however, visualization was limited. Because hemostasis could not be achieved, he underwent emergency digital subtraction angiography (DSA), which showed contrast extravasation from a gastric artery pseudoaneurysm, the inferior splenic artery, and a branch of the left gastric artery (Figure 5A).



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Figure 2 Selective digital subtraction angiography showed no extravasation of contrast medium in the gastric area. A: Digital subtraction angiography in March 2021; B: Digital subtraction angiography in September 2021.



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Figure 3 Treatment and disease status timeline. HCC: Hepatocellular carcinoma; TACE: Transcatheter arterial chemoembolization; CT: Computed tomography; RFA: Radiofrequency ablation; MRI: Magnetic resonance imaging; PD: Progressive disease; PR: Partial response; ATZ: Atezolizumab; BVZ: Bevacizumab.

FINAL DIAGNOSIS

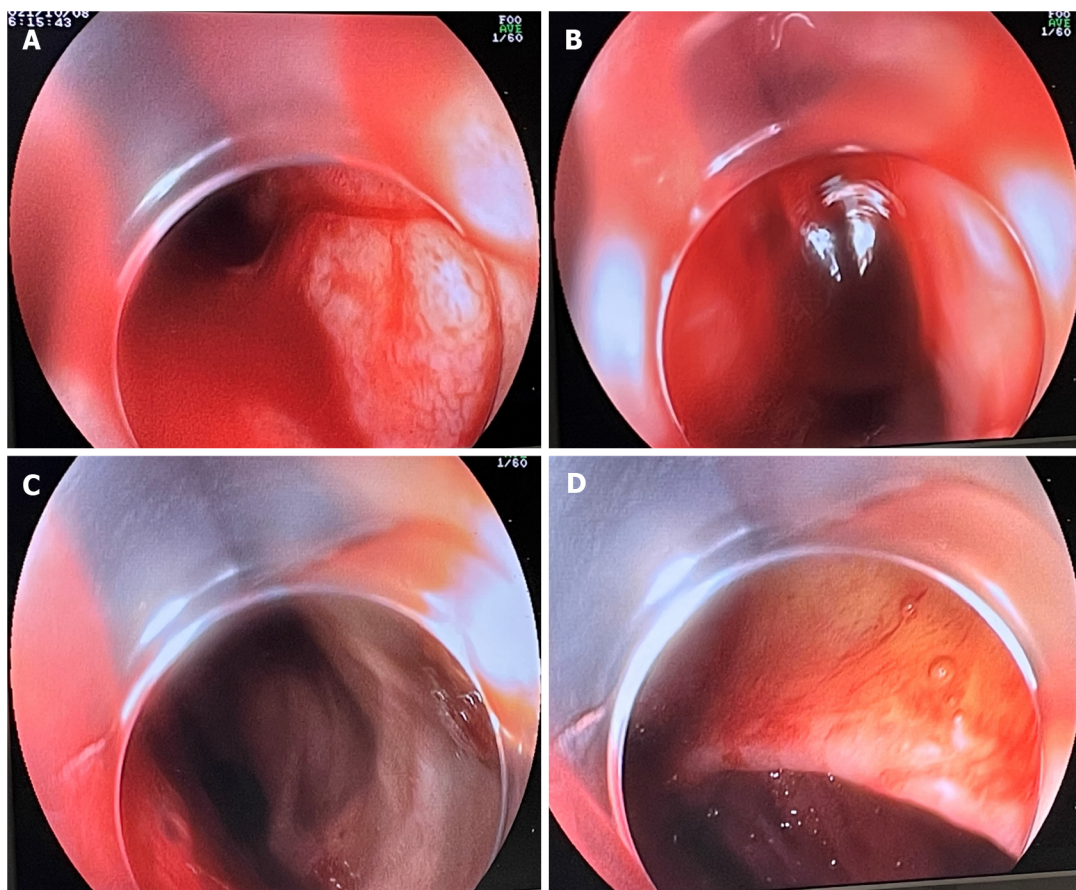
The final diagnosis was acute massive upper GI bleeding from a gastric pseudoaneurysm.

TREATMENT

The pseudoaneurysm was successfully embolized with a mixture of lipiodol (2 mL) and liquid glue (0.5 mL) (Figure 5B-D).

OUTCOME AND FOLLOW-UP

Although embolization resulted in hemostasis and marked improvement in general condition, the patient later developed liver failure and hepatic encephalopathy. Further treatment was discontinued at the family's request. Unfortunately, he died because of disease deterioration 6 d later.



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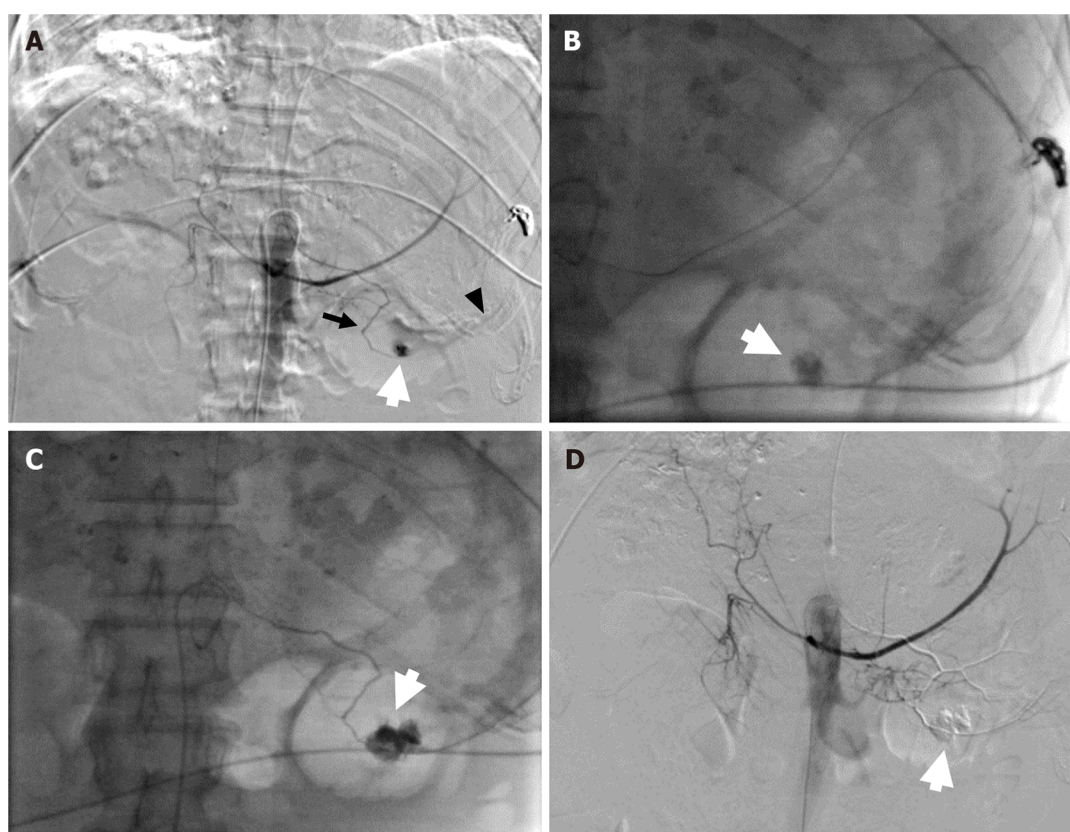
Figure 4 The findings of gastrointestinal endoscopy performed by the time of massive upper gastrointestinal bleeding. Visualization was limited because of massive fresh blood and blood clots within the stomach. A-C: No remarkable esophageal varices or red wale signs were observed in esophagus and fundus of stomach; D: No recurrence of gastric carcinoma or anastomotic bleeding was detected.

DISCUSSION

We report a patient who presented with massive bleeding after receiving ATZ + BVZ treatment for progressive HCC. Although endoscopy failed to detect a bleeding source, DSA revealed a gastric artery pseudoaneurysm and contrast extravasation from the inferior splenic artery and a branch of the left gastric artery. Hemostasis was achieved after successful embolization.

ATZ is a humanized immunoglobulin G1 monoclonal antibody which selectively targets programmed cell death ligand 1 on tumor-infiltrating immune cells or tumor cells and prevents ligand interactions with programmed cell death protein 1 and the costimulatory molecule B7-1 on activated T-cells. This enables inhibition of effector T-cells and induces tumor cell death[11,12]. ATZ is associated with a wide range of immune-related adverse events that can involve almost any organ[13]. In the IMbrave150 study[8], the most common ones were hepatitis (53%), rash (22%), and hypothyroidism (14%); incidence of GI bleeding was relatively low.

BVZ is a recombinant humanized monoclonal immunoglobulin G antibody which binds VEGF and blocks its interaction with receptors on endothelial cells to inhibit tumor angiogenesis and growth[14]. VEGF-A is an important growth factor which induces vascular permeability, stimulates extracellular matrix remodeling, and creates new blood vessels[15]. BVZ inhibits normal and pathological angiogenesis *via* targeting VEGF-A. In the IMbrave150 study[8], GI bleeding (3%), pulmonary hemorrhage (0.3%), and subarachnoid hemorrhage (0.3%) were adverse events which led to withdrawal of treatment. The cause of the gastric pseudoaneurysm in our patient remains unclear; however, based on the inhibitory effect of BVZ on VEGF and angiogenesis, BVZ may have been involved. Gastric artery pseudoaneurysms are rare and usually cause no symptoms; they are typically found after rupture[16]. Causes include pancreatitis, trauma, peptic ulcer, atherosclerosis, iatrogenic, and connective tissue disorders[17]. Computed tomography angiography is the most sensitive noninvasive diagnostic modality for detecting pseudoaneurysms[18]. The early diagnosis of gastric pseudoaneurysm by computed tomography angiography was unavailable because the patient had no related symptom or laboratory abnormalities until he suffered from massive upper GI bleeding. Shord *et al*[19] reported pseudoaneurysms of the left internal iliac artery and superior rectal artery, respectively, in two patients who received BVZ therapy for metastatic colorectal cancer. Our patient had no history of anticoagulant



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Figure 5 Emergency angiography. A: Selective digital subtraction angiography of the celiac trunk showed extravasation of contrast medium (white arrow) from the inferior splenic artery (black arrow), a branch of the left gastric artery (black arrow head), and a pseudoaneurysm of the gastric artery; B and C: The pseudoaneurysm (white arrow) was embolized using liquid glue and lipiodol; D: After embolization, the pseudoaneurysm (white arrow) and active bleeding were no longer visible.

use or cardiovascular or other diseases associated with increased risk of bleeding. As a result, BVZ may have been the cause of his gastric artery pseudoaneurysm and bleeding. Moreover, deterioration of HCC can also be the cause of bleeding.

Because the patient had a remote history of gastric carcinoma and partial gastrectomy and the site of bleeding was in the stomach, recurrence of gastric carcinoma and anastomotic bleeding should be taken into consideration. Unfortunately, we did not perform endoscopy before ATZ + BVZ was administered or before bleeding began. GI endoscopy at the time of bleeding failed to detect the bleeding site because of limited visualization. However, the gastrectomy was performed approximately 30 years prior and the recurrence rate more than 10 years after curative gastrectomy is lower than 0.2% [20]. In addition, DSA performed before the massive bleeding occurred showed no pseudoaneurysm in the gastric area. Therefore, these possibilities are unlikely. In a meta-analysis of the risk of high-grade bleeding in patients with various cancers treated with BVZ, the risk was significantly higher in those who received 5 mg/kg per wk than those who received 2.5 mg/kg per wk [21]. However, none of the studies included in the meta-analysis examined patients with HCC. HCC patients typically receive doses of BVZ (15 mg/kg) and ATZ (1200 mg) on the same day administered every 3 wk [8]. BVZ dosing adjustments have not been established at present. Our patient received the standard recommended BVZ dose; therefore, it is not likely to have been the cause of bleeding.

Acute GI bleeding from varices or nonvariceal lesions can be fatal in patients with cirrhosis or HCC. Careful monitoring and appropriate intervention are important. Visceral artery pseudoaneurysms require immediate treatment because their rupture rate is high [22] and endovascular embolization using coils and/or liquid glue is effective. In our patient, owing to his poor physical condition and the massive degree of bleeding, embolization was successfully performed using a mixture of liquid glue and lipiodol.

In HCC patients undergoing treatment with ATZ + BVZ, we recommend GI endoscopy before and after therapy. Patients with a high risk of bleeding should be followed for 3 to 6 mo [23]. Any pseudoaneurysms identified should be embolized under DSA guidance.

CONCLUSION

In this study, we report a case of massive GI bleeding from a gastric pseudoaneurysm in patient after ATZ + BVZ treatment for HCC. Awareness of this rare and life-threatening complication allows specific diagnostic evaluation and timely intervention. Angioembolization of the pseudoaneurysm guided by DSA is preferred whenever a pseudoaneurysm becomes apparent.

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FOOTNOTES

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