pISSN 2287-2728
eISSN 2287-285X

CMH

http://dx.doi.org/10.3350/cmh.2014.20.3.300
Clinical and Molecular Hepatology 2014;20:300-305

Case Report

Gastrectomy for the treatment of refractory gastric ulceration after radioembolization with ^{90}Y microspheres

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Transcatheter arterial radioembolization (TARE) with Yttrium-90 (^{90}Y)-labeled microspheres has an emerging role in treatment of patients with unresectable hepatocellular carcinoma. Although complication of TARE can be minimized by aggressive pre-evaluation angiography and preventive coiling of aberrant vessels, radioembolization-induced gastroduodenal ulcer can be irreversible and can be life-threatening. Treatment of radioembolization-induced gastric ulcer is challenging because there is a few reported cases and no consensus for management. We report a case of severe gastric ulceration with bleeding that eventually required surgery due to aberrant deposition of microspheres after TARE. **(Clin Mol Hepatol 2014;20:300-305)**

Keywords: Gastrectomy; Gastric ulcer; Hepatocellular carcinoma; Radioembolization; Yttrium-90

INTRODUCTION

The first line therapeutic modality for non-surgical patients with large and multifocal hepatocellular carcinoma (HCC) who do not have vascular invasion or extrahepatic spread is transcatheter arterial chemoembolization (TACE). However, transcatheter arterial radioembolization (TARE) with Yttrium-90 (^{90}Y)-labeled microspheres has an emerging role in treatment of unresectable HCC patients with or without portal vein thrombosis, or as a bridge to transplantation.[1,2] Radioembolization refers to injection of embolic beads loaded with radioisotopes using transarterial technique. Microsphere radioembolization allows the delivery of radioactive beads directly to the site of malignancy, thereby minimizing toxicity to adjacent organs. Despite direct delivery to tumor site, complications still occur when the microembolic effect or radiation injury occurs in organs other than liver. Reported side effects are predominantly constitutional symptoms such as fever while others are gastrointestinal ulceration or bleeding, cholecystitis, pancreatitis, radiation pneumonitis and hepatic decompensation.[3] Herein, we report a case of severe gastric ulceration with bleeding that eventually required surgery due to aberrant deposition of microspheres.

Abbreviations:

^{90}Y, Yttrium-90; CT, computed tomography; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; MAA, macroaggregated albumin; RFA, radiofrequency ablation; Tc, technetium; RGA, right gastric artery; TACE, transcatheter arterial chemoembolization; TARE, transcatheter arterial radioembolization; TGF, transforming growth factor

*This study was supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).

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Received : Oct. 3, 2012 / **Revised :** Nov. 19, 2012 / **Accepted :** Nov. 21, 2012

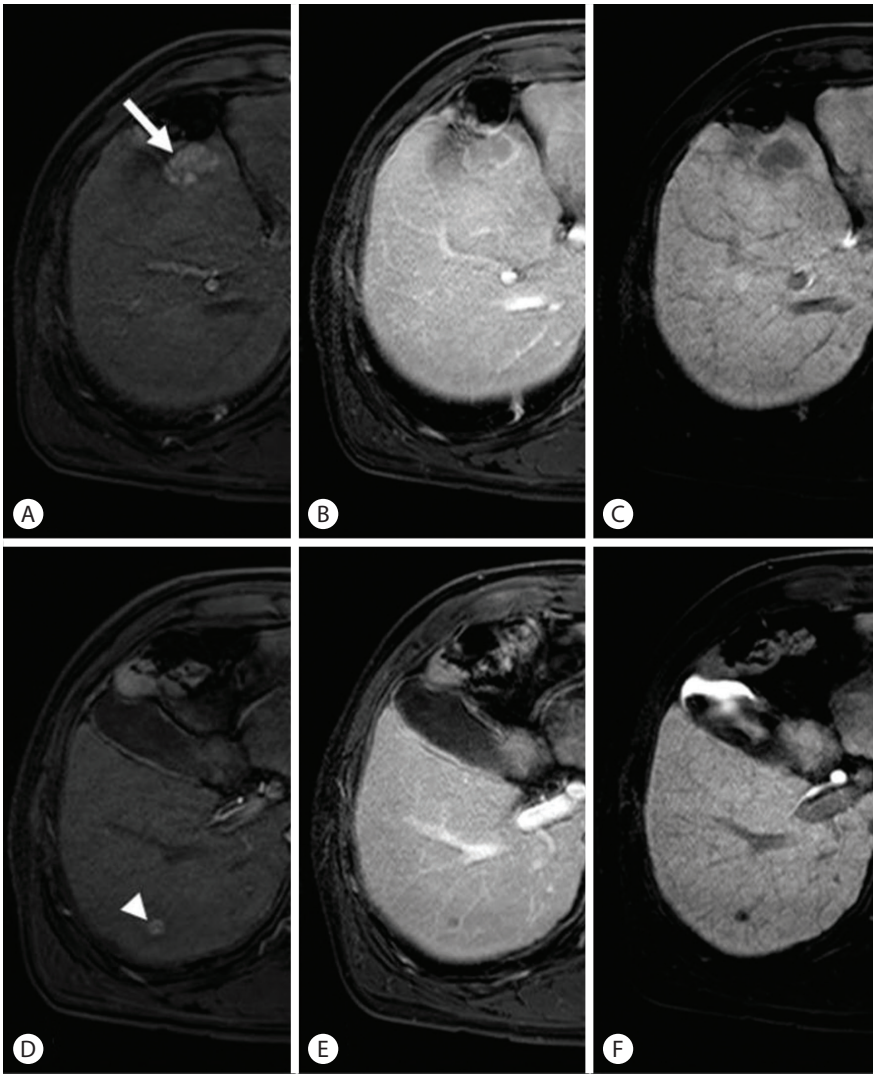

Figure 1. Gadoxetic acid-enhanced liver MRI before TARE. The image reveals a 2.7 cm sized arterial enhanced nodule (arrow) in segment 4 with delayed washout (A, B, C). Another nodule (arrowhead) measuring 0.6 cm was noted in segment 7 (D, E, F). (A, D) Arterial phase. (B, E) E Portal venous phase. (C, F) Hepatobiliary phase.

CASE

A 67-year-old male, inactive hepatitis B virus (HBV) carrier (HBeAg negative with undetectable serum HBV DNA level), was admitted for further evaluation and treatment of hepatic masses. He had a relatively good performance status (grade 1). Laboratory tests showed serum albumin level of 3.7 g/dL, bilirubin level of 1.5 mg/dL, and prothrombin time international normalized ratio of 1.40. Neither ascites nor hepatic encephalopathy was found, which was compatible with Child-Pugh class A. Serologic marker for hepatitis C was negative. Serum alpha-fetoprotein level was increased to 1,298 ng/mL. Dynamic enhanced computed tomography (CT) revealed underlying liver cirrhosis with a hepatic mass measuring 2.7 cm in segment 4 and another lesion measuring 0.6 cm in segment 7 with typical patterns of arterial enhancement and delayed washout. Gadoxetic acid-enhanced liver magnetic resonance imaging showed slightly high signal intensity in the T2 and diffusion-weighted image with a defect in 20-minute delayed image for these two lesions (Fig. 1). These findings were compatible with HCC (T3N0M0), stage III.

Radiofrequency ablation (RFA) or TACE can be considered as locoregional treatments for these unresectable HCC nodules in this cirrhotic patient who had no living donor for liver transplantation. However the lesion in segment 4 located adjacent to small bowel and gallbladder, the interventional radiologist concerned about the risk of ablation-related complications and recommended TARE. Subsequently, planning studies for TARE were done according to our hospital TARE protocol. Angiographic studies to detect the variation of arterial vessels that distribute to the liver and other vessels that give access to extrahepatic organs as well as the re-

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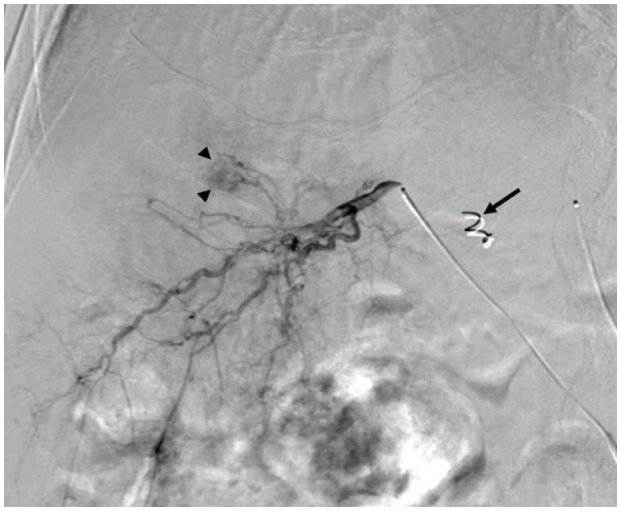

Figure 2. Right hepatic angiogram reveals a hypervascular tumor staining (arrowheads) at segment 4. Note metallic coil (arrow) for embolizing the gastroduodenal artery before TARE.

view of the portal vein patency were done. After angiographic study, technetium (Tc)-99m macroaggregated albumin (MAA) was injected to determine the degree of shunt to the lung as well as gastrointestinal tract. The calculated extrahepatic shunt was 10.71%. In the pre-evaluation study, no contraindication was observed for the angiography and Tc-99m MAA test.

Three weeks later, TARE was performed. Prior to the embolization, empirical coil embolization for the gastroduodenal artery was done to prevent complication of non-target lesion. A dose of 0.85 GBq of ^{90}Y microspheres was delivered via left hepatic artery and right posterior segmental artery, through 2.7F microcatheter (Fig. 2). Immediately after the procedure, patient complained severe abdominal pain but post-TARE scan without injection of Tc-99m MAA demonstrated tumoral uptake of ^{90}Y but no gastrointestinal uptake was observed. Pain was controlled with tramadol and the patient was discharged one week after TARE. However, the pa-

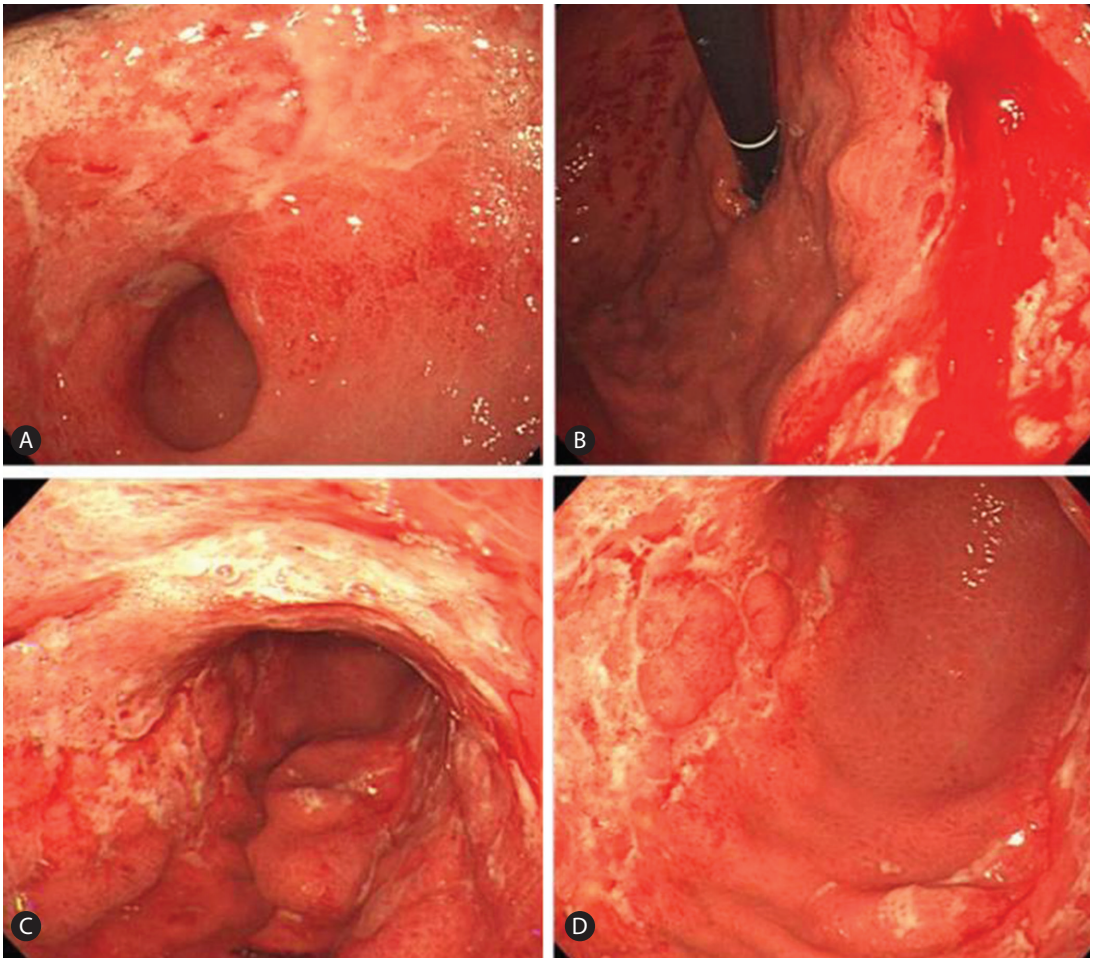

Figure 3. Upper endoscopy. Huge geographic ulceration with easy-touch bled, denudated friable mucosae is noted along the lesser curvature of gastric antrum and mid-body.

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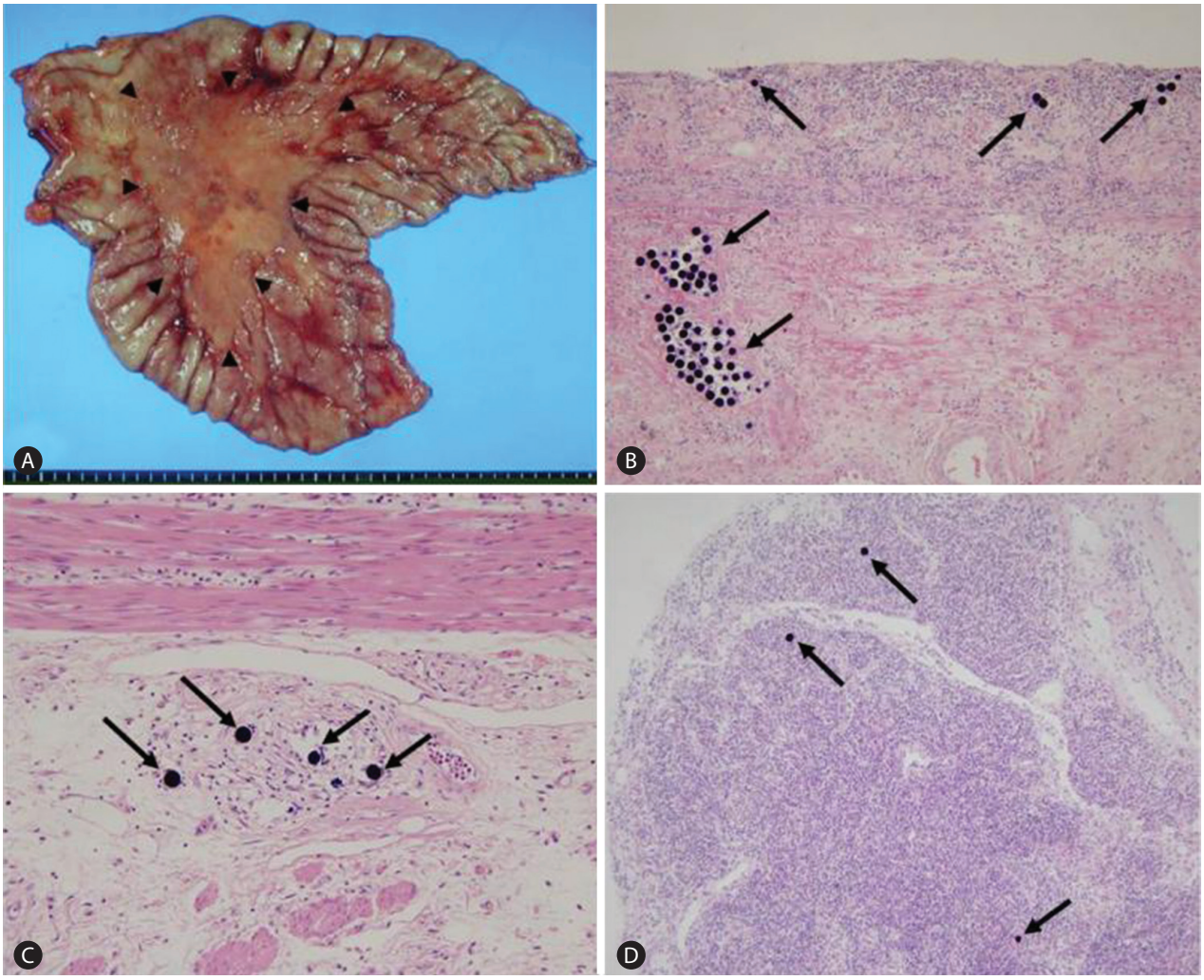

Figure 4. Resected specimen and microscopic observation of the lesion after subtotal gastrectomy. Grossly diffuse ulcerative mucosal surface (arrowheads) is noted (A). Gastric ulceration and scattered microspheres (arrows) are found within whole gastric layers (hematoxylin and eosin [HE] stain; original magnification, ×200; (B) mucosa and submucosa, (C) subserosa). Deposition of microspheres (arrows) is also shown in perigastric lymph node (D) with reactive hyperplasia of lymph node (HE stain; original magnification, ×200).

tient was readmitted due to severe abdominal pain four days after discharge. Upper endoscopy revealed geographic active ulcer at the lesser curvature of gastric antrum and mid-body. Histopathologic findings of endoscopic biopsy showed several deposited microspheres without evidence of *Helicobacter pylori* infection. Gastric ulcer was treated with full ulcer medications including an intravenous bolus followed by continuous-infusion of proton pump inhibitor. Follow-up enhanced computed tomography which was performed one month after TARE showed diffuse gastric wall thickening of antrum and lower body while HCC nodules in segment 4 and 7 were completely treated without recurrence. As abdominal pain failed to resolve with continuous medications, follow-up upper endoscopy was done two weeks later. Worsening of ulcerative mucosal lesions with exudative bases accompanied by diffuse mucosal friability and easy-touch bleeding were noted. Three additional endoscopic examinations were done to assess the lesions, but the aforementioned ulcers as well as the territory of the lesion were not grossly changed (Fig. 3).

Surgical intervention was recommended due to persisting excruciating abdominal pain and refractory endoscopic findings, and finally, subtotal gastrectomy was performed three months after TARE. Gross pathologic specimen revealed diffuse ulceration with multiple scattered microspheres deposited in the whole gastric layers, vessels and perigastric lymph nodes (Fig. 4). The patient's symptom resolved after surgery and he was discharged two weeks later without any complication. The patient remains in good health

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without HCC recurrence after 30 months of gastrectomy.

DISCUSSION

Patients treated with chemoembolization for the treatment of HCC are reported to show similar survival time to those treated with ^{90}Y labeled microspheres radioembolization. One of the advantages of TARE is decreased embolic effect compared to TACE allowing treatment for those with main portal vein thrombosis. Furthermore, TARE resulted in longer time-to-progression and less toxicity than TACE.[4,5] Although complication rate may be less than TACE, gastrointestinal ulceration following TARE can lead to fatal bleeding, small bowel obstruction and perforation.[6] These complications occur due to non-target spheres distributed to aberrant vessels supplying gastrointestinal tract as well as changes in flow dynamics during infusion. Early studies showed high incidence (25%) of gastrointestinal ulceration, but the incidence dropped to less than 5% after more extensive angiographic search to assess the hepatic vasculature and its collateral vessels that supply gastrointestinal tract as well as lung shunting.[6-8] One of the studies reported that median ulceration rate was 8%, ranging from 0 to 20%, with 6% (0.4% of the entire cohort) requiring surgery.[6]

Prior to treatment, angiographic study is performed to minimize any complication. According to study by Song *et al*. based on 250 patients,[9] the most common aberrant artery was the right gastric artery (RGA) 78.4% and left gastric artery 17.2% while hepatic falciform artery, posterior superior pancreaticoduodenal artery and left inferior phrenic artery comprising the rest of the aberrancy. In our case, celiac and superior mesenteric arteries were evaluated, especially the right, and left gastric arteries which supply gastrointestinal tract with high aberrancy rate but no aberrant vessel was observed. Microcoil embolization is the most widely adopted method for preventing extraheptic arterial embolization, while balloon occlusion technique is another choice to occlude hepatopetal flow in the common hepatic artery which is less commonly used.[10-12] Finally, Tc-99m MAA is injected into hepatic artery followed by single photon emission computed tomography to determine the degree of pulmonary and extrahepatic shunting.[7,8] All these planning studies were performed in this patient and coiling was done for gastroduodenal artery but not for RGA before TARE. Despite aggressive pre-evaluation, 3-5% incidence of gastrointestinal complication occurs due to failure in detecting smaller vessels or collaterals developing in several weeks after empirical coil embolization.[13] Another possibility of gastrointestinal injury is due to dynamic changes which may occur from embolic effect of microspheres due to slowing of antegrade flow that increases the risk of particle reflux.[14] Besides this, catheter stimulus may cause vessel spasm, infrequently. In this case, complication could have been prevented if the RGA was coil embolized prior to radioembolization considering the high incidence of gastric ulceration due to reflux of particles into RGA. Small collateral vessels and hypertrophy of other vessels might develop after coil embolizations which were unnoticed during the procedure. Our case emphasizes the importance of finding collateral vessels meticulously even after coil embolization to ensure that there is no other vessels that might lead to reflux of particle into vessels feeding gastrointestinal tract.

Symptoms of gastrointestinal complications include nausea, vomiting and abdominal pain. Time to diagnosis varies from less than 1 month to over 9 months and mean time to diagnosis is reported to be 3.2 months.[8] Therefore gastric ulceration due to TARE should be suspected if severe abdominal pain persists and clinicians must not hesitate to perform endoscopy. Antral and pyloric channel ulcerations with extension to duodenum are common.[13] Endoscopic findings including erosions, erythema, exudation, friability and bleeding are not specific findings, so biopsy is required to definitely distinguish radioembolization-induced ulceration from other causes of ulcer. The characteristic finding that allows diagnosis of radioembolization-induced ulceration is microsphere particles lodged in vessels of hematoxylin and eosin stained specimen. Other supporting findings of radioembolization-induced ulceration are apoptosis, epithelial flattening, and glandular cystic dilatation to nuclear atypia, capillary ectasia, and prominent endothelial cells.[15] Since radioembolization associated ulceration is diagnosed pathologically, repeated endoscopic examinations and multiple biopsies are needed if initial biopsy reveals negative result.

Treatment of radioembolization-induced gastric ulcer is challenging because there is no consensus for management. Currently, the treatment is no different from medications that are prescribed for peptic ulcer disease, namely acid suppression. Proton pump inhibitor is the first line of therapy but response rate is low. Understanding the mechanism of ulceration may explain the low response rate of treatment. Ulceration result from ischemic injury due to occlusion of arteries supplying gastrointestinal tract, direct toxic effect of radiation or both. Radiation destroys parietal cells leading to decreased gastric secretion, thus unlike peptic ulcer disease that originates from acid-induced mucosa, injury, acid suppression treatment may not be effective.[16] Additionally radioembolization induced ulcers occur at the serosal surface not mucosal

http://dx.doi.org/10.3350/cmh.2014.20.3.300

surface causing lack of response of acid suppression therapy which acts primarily at the mucosa.[3] Radiation enteritis is known to be caused by excessive stimulation of transforming growth factor (TGF)-β1 which leads to fibrosis and organ failure. Interferon-γ inhibits the effect of TGF-β1.[17] Therefore, pentoxyfylline, a phosphodiesterase inhibitor that reduces inflammation mediated by cytokines including TGF-β can be effective in radioembolization associated gastric ulcer.[7] Besides this, the effectiveness of anti-inflammatory agent such as sulfasalazine and antioxidant that reduces radiation induced free radical formation such as tocopherol can be considered as treatment options.[8] Since there is no one validated effective treatment, outcome can be fatal if appropriate time for surgical approach is missed. Early surgical intervention should be considered when abdominal pain persists and mucosal ulceration aggravates in endoscopic findings.

In summary, radioembolization-induced ulcer can be irreversible and can be life-threatening and therefore, aggressive pre-evaluation angiography and preventive coiling of aberrant vessels should be done before performing the procedure. This is the first reported, preceptive case of radioembolization-induced severe gastric ulcer in Korea which emphasizes the operator perception of the possibility of reflux into gastrointestinal artery and the need of surgery when gastric ulcer is refractory to medical treatment.

Conflicts of Interest

The authors have no conflicts to disclose.

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