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Case study

Microvascular injury in persistent gastric ulcers after yttrium-90 microsphere radioembolization for liver malignancies☆

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Summary Yttrium-90 microsphere radioembolization (^{90}Y MRE) is a therapy for liver malignancies by permanently implanting ^{90}Y-containing microspheres into tumors via hepatic artery. The etiology of persistent gastric ulcerations in patients presenting months after treatment remains unclear. Three patients who presented with gastric ulceration 4 to 13 months after ^{90}Y MRE were examined by esophagogastroduodenoscopy and biopsies. Pathological examinations showed multiple ^{90}Y microspheres scattered within the lamina propria and submucosa. Most of the microspheres were distributed in a linear fashion, consistent with an intravascular location; however, the vascular lumen and endothelial cells were not present. The microspheres were surrounded by fibrotic tissue infiltrated by chronic inflammatory cells and rare neutrophils. Epithelial granulation without pititis and miniaturized glands with intervening fibrosis were noted, compatible with chronic ischemic changes. These findings suggest that the persistent gastric ulceration is a result of localized ischemic injury in response to ^{90}Y MRE–induced vascular damage.

1. Introduction

Yttrium-90 (^{90}Y) microsphere radioembolization is a therapy permanently implanting resin or glass microspheres containing ^{90}Y to infarct tumors. ^{90}Y is a pure β-emitter with an average β emission of 0.9367 MeV and a mean tissue penetration of 2.5 mm with a maximum of 11 mm. The liver is particularly amenable to ^{90}Y brachytherapy due to its

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distinctive dual-blood supply, favorably distributing radioactive pellets into tumor through the hepatic artery and sparing nonneoplastic liver tissue. Gastric complications are detected in 4% to 27% of patients treated with ^{90}Y microsphere radioembolization for liver malignancies [1,2]. The misrouting of radioembolic microspheres into the gastointestional mucosa is a major cause of complications, with reports of ulceration presenting as far out as 4 months after ^{90}Y microsphere radioembolization [3–6]. It is unclear why patients develop delayed gastric ulcerations months later, given that the half-life of ^{90}Y of 64 hours limits completed radiotherapeutic delivery within 14 days after implantation. Here, we investigated the pathological changes of the gastric mucosa in 3 patients with delayed gastric ulceration after ^{90}Y microsphere radioembolization for liver cancer. Our findings suggest that chronic ischemia resulting from vascular damage in response to misplaced ^{90}Y microspheres is a crucial contributing factor to the pathogenesis of anti–acid-resistant and persistent gastric ulceration in this setting. Identification of the causative mechanism will lead to better management strategies for these patients.

2. Materials and methods

2.1. Participants

2.1.1. Case 1

A 69-year-old man who was diagnosed 4 years prior as having poorly differentiated cholangiocarcinoma presented with melena for 3 days. He was treated with multiple chemoembolization and ^{90}Y microsphere radioembolization at the University of Illinois Hospital and Health Sciences System at Chicago, IL. Esophagogastroduodenoscopy showed a 1-cm nonbleeding ulcer within the lesser curvature of the fundus, which was biopsied and for which the patient was prescribed proton pump inhibitors.

The patient returned to the clinic 10 months later, presenting with a weeklong history of abdominal pain and distention exacerbated by food intake. Esophagogastroduodenoscopy showed that the ulcer had doubled in size. A biopsy was obtained, and treatment with proton pump inhibitor continued.

2.1.2. Case 2

A 61-year-old man who was treated with ^{90}Y microsphere radioembolization for unresectable cholangiocarcinoma 4 months prior presented for esophagogastroduodenoscopy for follow-up of previously diagnosed Barrett esophagitis and *Helicobacter pylori* gastritis. A 2-cm ulcer was identified within the prepyloric antrum area. A biopsy was performed.

2.1.3. Case 3

A 51-year-old woman with a medical history of leiomyosarcoma originating from her left retroperitoneum was found to have multiple liver metastases. She was treated with ^{90}Y microsphere radioembolization with partial response in tumor size reduction. The patient subsequently underwent radiofrequency ablation and resection of liver nodules after treatment with ^{90}Y. The patient presented with significant weight loss, persistent nausea, and abdominal pain without relief despite antacid intake 9 months after ^{90}Y microsphere radioembolizaton. Esophagogastroduodenoscopy showed nonbleeding ulcers within the antrum and angularis, which were biopsied. Follow-up esophagogastroduodenoscopy performed 2 months later revealed numerous gastric ulcerations within the distal body, proximal antrum, and prepyloric antrum with extension unto the pyloric channel. The mucosa appeared pale and mildly atrophic. Biopsies were performed.

2.2. Histopathologic and immunohistochemical studies

All biopsies were 4-um-thick formalin-fixed, paraffin-embedded tissue sections. Normal gastric tissue obtained from a gastric sleeve surgery served as control. Standard immunohistochemical stains were performed for *H pylori* (SP48, rabbit monoclonal antibody; Ventana Medical System, Tucson, AZ) and for platelet endothelial adhesion molecule marker, CD31 (JC70, mouse monoclonal antibody; Ventana Medical System Inc).

3. Results

3.1. Clinical summary

Three patients, 2 male and 1 female, with ages ranging from 51 to 67 years, were treated with ^{90}Y microsphere radioembolization for unresetable cancers in the liver, including cholangiocarcinoma and metastatic leiomyosarcoma. These 3 patients were found to have gastric ulcers at 13 (case 1), 4 (case 2), and 9 months (case 3) after ^{90}Y microsphere radioembolization. The gastric ulcers appeared to be persistent and, in 1 case, progressed in size and severity of symptoms despite use of antacid medications. Of note, case 1 was found to have persistent gastric ulceration lasting for 2 years after ^{90}Y therapy as determined by serial esophagogastroduodenoscopy and subsequent biopsies.

3.2. Pathological findings

Microscopic examination of the gastric mucosa showed common histologic features in these 3 cases (Table). All cases had multiple, monomorphic, round, purple, ^{90}Y microspheres, ranging from 50 to 80 μm in diameter, scattered within the lamina propria and the submucosal layer. Most of the microspheres were distributed in a linear fashion following an intravascular distribution (Fig. 1A) with obliteration of the vascular lumen and absence of the