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Case and Review

Recurrent Upper Gastrointestinal Bleeding due to Radiation-Induced Hemorrhagic Gastroduodenal Ectasia: A Review of Current Treatment Options for Radiation-Induced Gastric Injury

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Keywords
Case report · Radiation · Gastric antral vascular ectasia · Gastroinstestinal bleed · Anemia · Ectasia

Abstract
Introduction: Acute upper gastrointestinal bleeding is one of the most common medical emergencies that present to the hospital, and delineating the underlying etiology is essential to provide adequate definitive treatment. The purpose of this case report was to review the diagnosis and treatment of a rare complication known as radiation-induced hemorrhagic gastritis (RIHG) that can occur in patients with prior radiation exposure. The motivation for this study arose from the identification of a case within our institution. ***Case Presentation:*** The study involved a review of the diagnosis and management of a patient who presented with anemia and recurrent episodes of gastrointestinal bleeding at our institution after undergoing treatment for metastatic biliary adenocarcinoma. With the advent of new therapies, we aimed to investigate the various techniques utilized to manage these patients and highlight the importance of maintaining a high index of suspicion for RIHG as a potential etiology of gastrointestinal bleeding in patients with a relevant medical history of radiation exposure. Despite the literature review, we found that there is a lack of guidelines in the approach to the management of these patients. ***Conclusion:*** This case report underscores the rarity of radiation-induced gastritis and

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the complications that may arise from its diagnosis, including recurrent GI bleeding. Further investigation into identifying definitive treatment and creating guidelines for its management is desperately needed.

Introduction

Radiation-induced hemorrhagic gastritis (RIHG) is a rare complication postradiation therapy that can result in life-threatening upper gastrointestinal bleeding (GIB). We present a case of a patient who developed this unusual complication due to underlying radiation-induced gastroduodenal vascular ectasia (GDVE) which led to multiple episodes of recurrent GIB and symptomatic anemia. Our study aimed to highlight the various treatment options available and the importance of maintaining a high index of suspicion for RIHG as a potential etiology of GIB in patients with relevant medical history of radiation exposure. This case was submitted utilizing the CARE Checklist which has been completed by the authors for this case report and attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000538965).

Case Description

A 55-year-old Hispanic female with a past medical history of metastatic biliary adenocarcinoma (diagnosed in June 2021), complicated by a large lymphatic mass involving the confluence of the common hepatic duct, periportal lymph node, perinodular and periductal soft tissue, and perineural invasion, presented to the emergency department with melena and lightheadedness.

Her medical history was significant for previous exploratory laparotomy with hepatic and extrahepatic bile duct resection and hepaticojejunostomy in September 2021, which was complicated by biliary leak and necessitated drain placement, with the drain subsequently removed in January 2022. She also underwent concurrent treatment with capecitabine and 25 fractions of intensity-modulated radiation therapy to the gallbladder and extrahepatic site.

Of note, she had a history of multiple endoscopic evaluations and admissions following completion of chemoradiotherapy in January 2022 prior to this presentation for similar complaints of GIB. Previous upper endoscopy was notable for a gastric antral ulcer with oozing which was treated with a clip and bipolar cautery. However, 5 days later she continued to have episodes of melena and underwent two subsequent endoscopies another 5 days apart which revealed mucosal oozing in the gastric antrum, treated with argon plasma coagulation (APC), and a large, persistent pyloric ulcer with active bleeding that was treated with clips and hemostatic powder to control refractory bleeding. Colonoscopy was unremarkable. She had no bleeding following her last procedure in October of that year and was discharged home on a proton pump inhibitor (PPI) and iron supplementation with plans for repeat endoscopy in the outpatient setting to ensure ulcer healing.

Following discharge from the hospital, she received multiple packed red blood cell transfusions with inappropriate hemoglobin response and continued lightheadedness. She has remained adherent with her PPI. She denied any nonsteroidal anti-inflammatory drug use, anticoagulant or antiplatelet use and had no history of tobacco or alcohol use.

On this admission, her laboratory values included hemoglobin 6.9 requiring a transfusion and iron deficiency. Gastroenterology was consulted, and she underwent repeat upper endoscopy in November that revealed a non-bleeding Forrest Class III pyloric gastric

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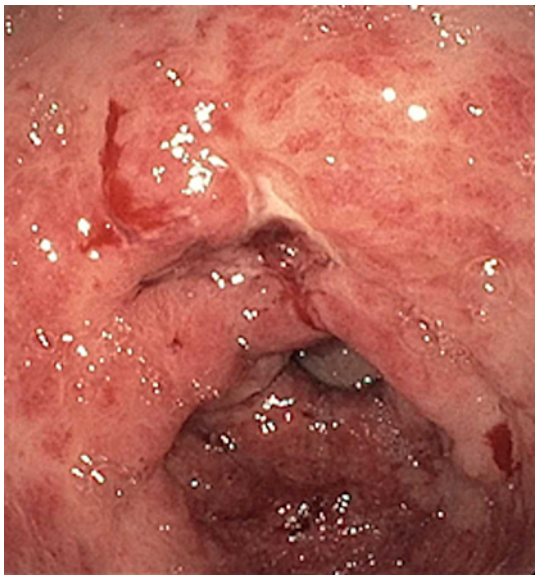

Fig. 1. Upper endoscopy demonstrating a clean-based gastric ulcer with erythematous mucosa in the prepyloric region of the stomach.

ulcer with a clean base (Fig. 1), erythematous mucosa in the cardia (Fig. 2), body, and antrum, which was treated with APC and erythematous duodenopathy in both the first and second part of the duodenum (Fig. 3). Biopsies were performed, and histology revealed features of ulceration, fibrosis, ectatic vessels with thrombi, and reactive changes (Fig. 4a, b), which although not specific are compatible with radiation-induced hemorrhagic GDVE. She remained hemodynamically stable post the procedure and was discharged home with plans for repeat endoscopy in the outpatient setting.

Discussion

Damage of the upper gastrointestinal (GI) tract may occur as a sequela of radiotherapy of tumors of the GI tract or of adjacent structures [1, 2]. RIHG, an uncommon condition, is typically a diffuse process with multiple bleeding sites that may lead to severe GIB, making it a potentially life-threatening complication of radiation therapy. RIHG is difficult to manage and may be classified as an acute/early phase complication versus a chronic or late phase complication depending on the time of presentation after therapy [3].

During the acute phase, which occurs typically within 3 weeks to 3 months after onset of therapy, patients may present with predominant symptoms of nausea and vomiting. Changes found on endoscopy are typically in the gastric antrum, revealing new or worsened dark red spots and patches, as well as exudative changes and ulcers [4]. Addressing these changes early in the acute period may result in reversibility [5]. Meanwhile, in the subacute or chronic phase which occurs greater than 3 months after radiation therapy, patients may present with abdominal pain and endoscopic findings showing fusion of red plaques, flattening of folds, annular ulcers, and telangiectasia, and persistent ulcers leading to perforation, bleeding, or antral stenosis in the irradiated area [4]. These changes are likely to be irreversible in this patient population [5]. It is important to keep in mind that the reversibility of the injury induced by radiation on the gastric mucosa is not only dependent on the acuity but also the dose of radiation used in treatment. While low-dose radiation (up to 15 Gy) can cause reversible gastric injury, high-dose radiation is likely to lead to irreversible changes [6].

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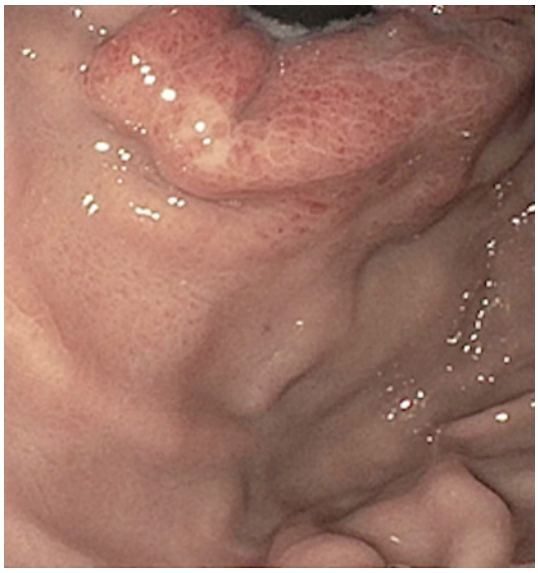

Fig. 2. Erythematous mucosa in the cardia seen on endoscopy.

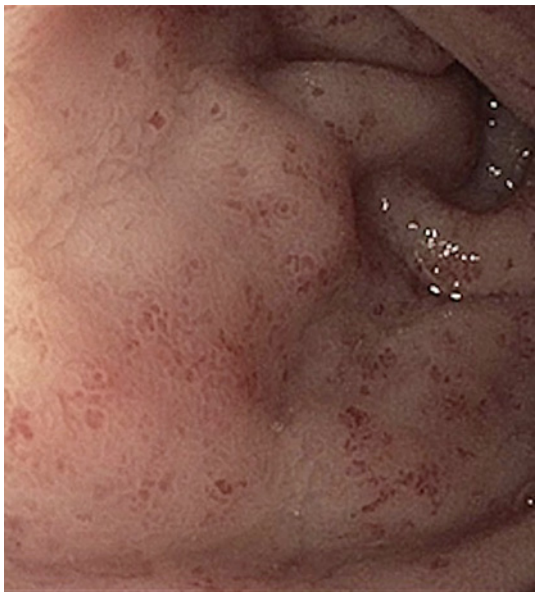

Fig. 3. Erythematous duodenopathy seen on endoscopy.

In terms of onset, the literature indicates that radiation-induced gastritis often presents between 1 and 12 months postradiation, with peak ulceration typically occurring within 1–2 months [7]. However, some sources suggest that the stomach generally develops radiation-induced mucosal damage 5–6 months after the completion of irradiation as seen in our case [8].

The underlying pathophysiology is characterized initially by acute inflammation of the gastric mucosa, and as the injury progresses, vasculopathy may evolve to progressive obliterative endarteritis and endothelial proliferation that leads to mucosal ischemia, ulceration, and telangiectasia [9]. The severity of damage is directly related to the high total dose and high daily fraction of radiation used [10]. The incidence of gastric ulcers due to radiation therapy is between 25 and 30% as the dose exceeds 45 Gy with risk of perforation when dose exceeds 60 Gy [11]. Our patient received a total dose of 50 Gy with concurrent adjuvant capecitabine and presented initially with anemia and GIB approximately 10 months

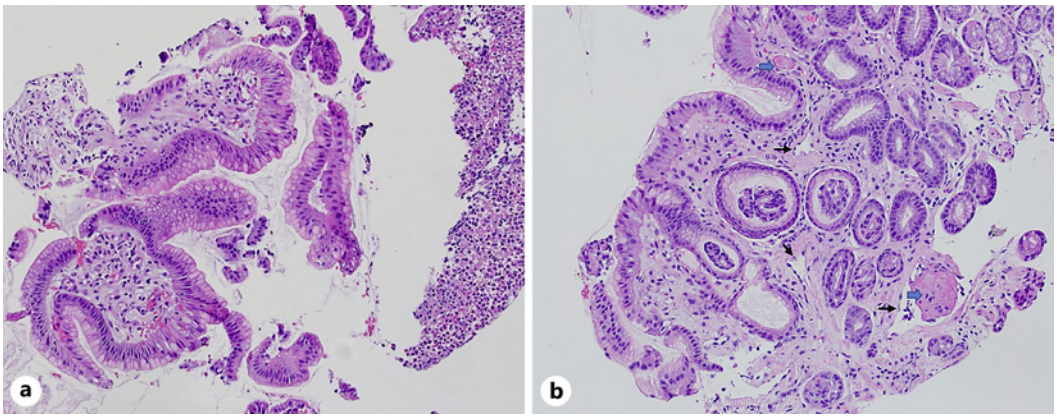

Fig. 4. a, **b** H&E sections show gastric mucosa with ulceration, lamina propria fibrosis, ectatic blood vessels (black arrows) with thrombi (blue arrows), and reactive epithelial changes (×200).

after completion of therapy. There is data in the literature that suggests that there is an association between radiation gastritis in the setting of capecitabine, a well-known radiation sensitizer similar to 5-fluorouracil. Both these agents are utilized in the treatment of GI malignancies, and there is evidence to suggest that not only malignant tumor but also normal tissue may be inadvertently radiosensitized, leading to an enhanced response and subsequent toxicity that may predispose to the development of radiation gastritis [12].

Various therapies have been described in the literature for patients with RIHG including medical therapy, endoscopic interventions, interventional radiology, and surgery. Medical therapy includes the use of antisecretory medications such as PPIs, sucralfate, glucocorticoids, and hyperbaric oxygen therapy. While there have been limited results with PPIs, Zhang et al. demonstrated that oral prednisolone due to its anti-inflammatory functions may reduce gastric mucosa damage and degeneration [13]. Another case report by Geun Yu et al. also suggested that the use of prednisolone treatment as a first line treatment can be used in these scenarios as the effect of steroids demonstrates similar efficacy to when used in radiation pneumonitis and severe radiation proctitis [9]. Hyperbaric oxygen is another option that has been reported in the literature, which works by serving as a stimulus to develop neovascularity in tissues rendered hypoxic because of late-onset radiation damage and is effectively used in radiation damage to the vagina, bladder, bowel, and rectum. Kernsitine et al. [14] proved that after 20 to 30 HBO exposures angiogenesis becomes complete and positive outcomes were reported in 2 patients suffering from this complication of radiation therapy.

Novel therapies such as bevacizumab have been used as a rescue agent in endoscopic refractory bleeding in patients with hemorrhagic radiation gastritis. It is an anti-VEGF humanized antibody successfully proposed for the treatment of severe epistaxis or GIB in hereditary hemorrhagic telangiectasia or vascular tumors and functions by inhibiting angiogenesis [15, 16].

For endoscopic techniques, APC has been described and works as a non-contact method of delivering high-frequency alternating current by means of ionized, electrically conductive argon gas. It is often used in the treatment of vascular lesions such as gastric antral vascular ectasia, malignant tumors, hemostasis of bleeding peptic ulcers, esophageal varices, and Barrett's esophagus [17]. Shukuwa et al. [18] described a case of RIHG successfully treated with APC. Liang et al. also demonstrated successfully stopping hemorrhage with repeated endoscopic APC combined with low-dose polyglycerol sclerotherapy for a patient with RIHG secondary to treatment for recurrent hepatocellular carcinoma [19]. Ross et al. [20] described combined therapy with APC and radiofrequency ablation for diffuse RIHG treatment. Kwak et al. [21] also investigated the use of APC

in those patients with GDVE which may itself be a subset of gastric vascular ectasia and was found to have short-term effectiveness and safety in the treatment of these patients. However, more studies are needed to confirm the effectiveness of APC in this population.

When RIHG results in severe recurrent bleeding not responsive to medical and endoscopic measures, surgery may represent a valid therapeutic option. Tatsis et al. [22] described a case of a 56-year-old man with hilar cholangiocarcinoma who developed bleeding secondary to RIHG. After several attempts at endoscopic hemostasis, the patient underwent subtotal gastrectomy with Roux-en-Y reconstruction with no further bleeding [22]. If surgery is not appropriate or possible, super selective transcatheter arterial embolization has been shown as a potential alternative for treatment of RIHG [23].

Despite the various therapies described, there are few case reports in the literature with RIHG due to its rarity as a complication. There is a clear need for more research into the management of these patients, particularly in both the acute and chronic phases of the disease. Further emphasis should be placed on prioritizing the development of standardized treatment guidelines, particularly for patients whose conditions are refractory to currently practiced therapies [9].

Statement of Ethics

Ethical approval is not required for this study in accordance with local and national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors declare that none of them has a conflict of interest regarding the publication of this paper.

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Author Contributions

Simone A. Jarrett performed the literature review, assisted in the initial manuscript, performed revisions, and is the article guarantor. Rushi Talati and Johann Hasbun performed the literature review and assisted in the initial manuscript. Rushi Talati and Scott M. Smukalla performed the endoscopic procedures, performed revisions, and edited the manuscript. Wenqing Cao performed pathologic and histologic evaluation. All authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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