A Case Series of Radiation-induced Hemorrhagic Gastroduodenitis

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Abstract:
Objective We examined the clinical course and treatment method of a case series of radiation-induced hemorrhagic gastroduodenitis with clinical signs.
Methods This was a single-center retrospective observational study.
Patients We included seven patients with radiation-induced hemorrhagic gastroduodenitis treated at our hospital between April 2014 and May 2020.
Results One male patient each had cancer of the head of the pancreas, bile duct cancer, hepatocellular carcinoma, and ureteral cancer, whereas two women had recurrent endometrial cancer and one woman had recurrent cervical cancer. The onset occurred 3-5 months after the end of radiation treatment. Endoscopic examinations showed a red edematous mucous membrane in a fragile condition stretching from the antrum of the stomach to the duodenum, with telangiectasia and ulcer. For endoscopic hemostasis, five patients underwent argon plasma coagulation (APC), which was successful in three patients. Two of these were being administered an antithrombotic at the time. One case resistant to conservative treatment required repeated transfusion for recurring hemorrhaging over a short period of time and therefore underwent surgical treatment. Thereafter, the postoperative course was favorable.
Conclusions Actively attempting hemostasis through APC and surgery is effective for treating radiation-induced hemorrhagic gastroduodenitis. The use of an antithrombotic agent might lead to a risk of repeated hemorrhaging. Therefore, repeated hemostasis through APC is crucial.
Key words: radiation-induced hemorrhagic gastroduodenitis, hemostasis, quality of life, argon plasma coagulation

(Intern Med 60: 2529-2535, 2021) (DOI: 10.2169/internalmedicine.6465-20)
rhagic gastroduodenitis treated at our hospital between April 2014 and May 2020. The criterion for the decision to treat was confirmation of hemorrhage causing chronic anemia or diminished quality of life (QOL), for which endoscopic examinations were used to confirm telangiectasia and erosion, as well as the absence of deep ulcers. The study was conducted in accordance with the Declaration of Helsinki (2013) after the protocol had been approved by the Ethics Review Committee of Osaka Medical College (Osaka Medical College Institutional Review Board approval no. 2901).

Table 1.

| No. | Sex   | Age (by 10 Years) | Underlying Disease | Irradiated Area | Irradiation Dose | Gastric Lesion | Duodenal Lesion | Initial Symptom | Comorbidty             | Antithrombotic Drug |
|-----|-------|-------------------|--------------------|-----------------|-----------------|----------------|-----------------|----------------|-----------------------|---------------------|
| 1   | Female| 70                | Endometrial Cancer, Recurrence | ParaAo | 60 | Gy Fr | Yes | Yes | Melena | Atrial Fibrillation | None |
| 2   | Male  | 80                | Ureteral Cancer    | ParaAo | 50 | Gy Fr | No | Yes | Melena | None | None |
| 3   | Male  | 70                | Biliary Cancer     | Primary Lesion (CRT) | 50 | Gy Fr | Yes | No | Grogginess | None | None |
| 4   | Male  | 60                | Pancreatic Head Cancer | Primary Lesion (CRT) | 50 | Gy Fr | Yes | No | Epigastric Pain | Atrial Fibrillation | Apixaban |
| 5   | Female| 30                | Cervical Cancer, Recurrence | Pelvis | 60 | Gy Fr | Yes | Somewhat | Epigastric Pain | Pelvic Venous Thrombosis | Edoxaban |
| 6   | Male  | 80                | Hepatocellular Cancer | Liver S | 48 | Gy Fr | No | Yes | Melena | Cirrhosis | None |
| 7   | Female| 60                | Endometrial Cancer, Recurrence | Pelvis | 60 | Gy Fr | No | Yes | Vomiting | Cirrhosis after Mitral Valve Replacement | Warfarin |

Results

The list of cases is presented in Table 1. There were four men (two in their 80s, one in his 70s, and one in his 60s) and three women (one in her 70s, one in her 60s, and one in her 30s). Table 1 includes the primary illnesses and radiation treatment details of all seven cases. Table 2 shows the clinical courses of all seven cases. Onset was three to five months after the end of radiation treatment. The initial symptoms were melena in three cases, epigastric pain in two cases, wobbling in one case, and vomiting in one case. During the initial examination, there was notable anemia [hemoglobin (Hb): 3.5-7.2 g/dL], but this was not pancytopenia due to bone-marrow suppression. The total number of units of transfusion administered ranged from 10 to 76 units. Endoscopic images confirmed a red edematous mucous membrane in a fragile condition stretching from the antrum of the stomach to the duodenum, together with telangiectasia and ulcer, and with most patients showing late reactions to radiation. For endoscopic hemostasis, APC was performed for five cases. Of the remaining two cases, one case naturally achieved hemostasis through observation (no. 2, Table 1). The other case required continued anticoagulant therapy, and given the increased risk of hemorrhaging, we only used thrombin spray without endoscopic hemostasis treatment (no. 7, Table 1). There were three cases in which hemostasis was achieved by endoscopic hemostasis and two cases in which hemostasis could not be achieved by endoscopic hemostasis, respectively. One case finally achieved hemostasis after nine rounds of APC (no. 1, Fig. 1). In terms of complications associated with endoscopic hemostasis, there was no complication when noncontact hemostasis was performed with APC, but there was one case of delayed perforation when contact hemostasis was performed with hemostatic forceps (no. 6, Fig. 2). Surgery was necessary for the resolution of a case resistant to conservative treatment, which repeatedly required transfusions over a short period of time, but this patient’s postoperative course was ultimately favorable (no. 3; Fig. 3). In terms of the use of antithrombotic agents, the woman in her 60s was taking warfarin following mitral valve replacement, the woman in her 30s was taking edoxaban (Daiichi Sankyo, Tokyo, Japan) for pelvic thrombosis, and the man in his 60s was taking apixaban (Bristol-Myers Squibb, New York, USA) for atrial fibrillation and clopidogrel for internal carotid artery stenosis. Two out of three cases experienced a recurrence of hemorrhaging after hemostasis, which was once again stopped with APC. Because the use of antithrombotic agents leads to a risk of hemorrhaging, it is important to repeat APC to achieve hemostasis. During the course of treatment, cases in which hemostasis was achieved were able to be shifted to outpatient treatment or at-home treatment, but those cases in which hemostasis was difficult or with delayed perforation experienced prolonged hospitalization, leading to a decreased QOL due to limitations placed on meals and activities (Fig. 4). In the present examination, the distribution of lesions and nutritional state were not related to hemostasis. We herein pre-
sent further details of three of the investigated cases below.

Case 1 (no. 1, Fig. 1): a woman in her 70s chiefly complained of melena. She had undergone surgery and postoperative chemotherapy performed for endometrial cancer (stage IVB). After 7 years, the cancer recurred in the paraaortic lymph node and for which radiation treatment was performed (60 Gy). Because melena was observed approximately 3 months subsequently, the patient was examined. Her Hb level decreased from 11.0 g/dL to 7.2 g/dL. She had a medical history of atrial fibrillation (no anticoagulant therapy), hypertension, and type II diabetes. A red hemorrhagic mucous membrane in a fragile condition was found ranging from the antrum to the descending part of the duodenum. A total of nine APC procedures were performed for recurring hemorrhaging, ultimately achieving hemostasis (Fig. 1). The subject was able to be converted to outpatient treatment and has not required any further transfusion for nine months.

Case 2 (no. 6, Fig. 2): a man in his 80s complained chiefly of melena. He had undergone radiation therapy (48 Gy/8 fr) for hepatocellular carcinoma (S5). Approximately 3 months later, melena was observed, and he was medically examined. His Hb level decreased from 11.0 g/dL to 6.9 g/dL. He had a medical history of type C liver cirrhosis. From the duodenum bulb to descending part of duodenum, a red edematous mucous membrane in a fragile condition was found, while an ulcer with exposed blood vessels was observed at the superior duodenal angle (Fig. 2a). In addition to APC, cauterization with hemostatic forceps was performed on the exposed blood vessels, but hemostasis was unsuccessful. A total of six hemostasis treatments were performed. On the 61st day of the illness, delayed perforation was noted, leading to peritonitis (Fig. 2b). The advancement of liver failure led to a deterioration of the case patient’s general condition and, after two months of hospitalization and treatment, he passed away.

Case 3 (no. 3, Fig. 3): a man in his 70s complained chiefly of wobbling. He had undergone chemoradiotherapy (50 Gy) for bile duct cancer (T3N1M0 stage IIIb). Approximately 5 months later, the patient visited our hospital for an examination with the chief complaint of general malaise. His Hb level decreased from 10.0 g/dL to 3.5 g/dL. He was immediately hospitalized. A red hemorrhagic mucous membrane in a fragile condition was found ranging from the antrum to the pyloric antrum (Fig. 3a) and repetitive attempts to achieve hemostasis with APC did not alleviate the anemia nor recurring hemorrhaging (Fig. 3b). As the case was considered to be resistant to conservative treatment, on the 28th of the illness, laparoscopically assisted distal gastrectomy was conducted (Fig. 3c). Pathologically, multiple sores and their reproduced images were found in the antrum and a scattered growth of collagen fibers and capillaries was observed in the lamina propria. Mild fibrous thickening was confirmed form the submucosa to the subserosa, which was consistent with the patient’s late reaction to radiation exposure (Fig. 3d, e). On postoperative day 33, the patient was discharged to recuperate for six months at home.

Discussion

To the best of our knowledge, the present paper is the first report to summarize clinical cases of radiation-induced hemorrhagic gastroduodenitis. The results of the present study indicate that actively attempting hemostasis through APC and surgery to treat radiation-induced hemorrhagic gastroduodenitis is effective. Because antithrombotic agents pose a risk of hemorrhaging, it is crucial to achieve hemostasis with repeated APC. Radiation enteritis is divided into early and late reactions, which appear by way of completely different mechanisms. An early reaction is marked direct and late reactions, which appear by way of completely different mechanisms. An early reaction is marked direct
damage to intestinal epithelial cells, while proliferation arrest and shrinkage of crypt epithelial cells, hyperemia of the mucous membrane due to reflux, thickening, sores, and hemorrhagic tendency are also observed. It is reversible, resolving spontaneously after several months without permanently reducing the QOL. On the other hand, a late reaction typically involves irreversible fibrosis of submucosa and arteriosclerotic changes. Vascular wall hypertrophy caused by endarteritis leads to microangiopathy and the characteristic endoscopic finding is red (2, 4, 5). The risks of radiation gastritis include a high total irradiation dose and fractional dose and tolerance dose for the stomach is said to be 45 Gy. An existing study conducted a prospective observational investigation of 123 cases in which chemoradiotherapy was performed to treat unresectable and advanced localized hepatocellular carcinoma and reported that there were 18 serious gastrointestinal complications (affecting 14.6% of cases) with an average onset of 74.3 days. Moreover, hemorrhaging was found in 13 out of 123 cases (10.6%) (6). When treating hemorrhagic cases, APC is considered to be effective for cases due to radiation gastritis (7) and radiation duodenitis (8-12); this is the first-line treatment option used at our facility as well. APC is able to discharge energy by dispersing current without contact, which makes it well-suited for operating near fragile mucous membranes. Liang et al. reported a case of hemorrhagic radiation-induced gastritis for which hemostasis was achieved by adding low-dose polidocanol sclerotherapy to APC (13). If a case is resistant to conservative treatment, surgical gastrectomy is effective. In the present study, one case was treated surgically and
showed a favorable course thereafter (14, 15). In terms of other treatments, the use of hyperbaric oxygenation for radiation damages is covered by the Japanese National Health Insurance Program and its use for radiation-induced gastritis has been reported to be effective (16, 17). As for drug options, cases showing efficacy for octreotide (18), glucocorticoid therapy (19), and growth hormone (20) have been reported. In terms of molecular targeted therapy, bevacizumab (a humanized anti-vascular endothelial growth factor monoclonal antibody) has been reported to be effective for suppressing neoangiogenesis in radiation gastritis (21). However, since this therapy inhibits the regeneration and repair of epithelial cells, it increases the risk of hemorrhage in the digestive tract (22). Meanwhile, sorafenib aggravates radia-
The course graph. A yellow line shows the course from the end of radiation treatment to the onset of radiation-induced hemorrhagic gastroduodenitis. A red line indicates hospitalization. A purple line indicates outpatient treatment with transfusion. A blue line indicates either outpatient or home treatment without transfusion.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement
We would like to extend our most sincere appreciation to the staff at the Endoscopy Center who provided their valuable support with hemostasis on a daily basis.

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