

[ ORIGINAL ARTICLE ]

## 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

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### Introduction

Regarding the treatment for radiation enteritis, although the 2016 Guidelines for Radiation Treatment Plan, which is the official guideline of the Japanese Society for Radiation Oncology, describes various gastrointestinal complications associated with radiation treatment of various types of cancers, however, insufficient details regarding prevention and treatment methods are included. Further, there are many reports on the efficacy of methods of endoscopic hemostasis such as argon plasma coagulation (APC) and hyperbaric

oxygen (1-3); however, there is no comprehensive report on radiation-induced hemorrhagic gastroduodenitis, and the clinical characteristics of this condition thus remains unclear.

In this study, we investigated the clinical courses of and the treatment methods used in cases of radiation-induced hemorrhagic gastroduodenitis with clinical signs presenting for management at our institution.

### Materials and Methods

We assessed the patients' background, treatment course, and outcomes of seven cases of radiation-induced hemor-

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**Table 1.**

No.	Age (by 10 Years)	Sex	Underlying Disease	Irradiated Area	Irradiation Dose	Irradiation Dose	Gastric Lesion	Duodenal Lesion	Initial Symptom	Comorbidity	Antithrombotic Drug
1	70	Female	Endometrial Cancer, Recurrence	ParaAo	60 30	Gy Fr	Yes	Yes	Melena	Atrial Fibrillation	None
2	80	Male	Ureteral Cancer	ParaAo	50 20	Gy Fr	No	Yes	Melena	None	None
3	70	Male	Biliary Cancer	Primary Lesion (CRT)	50 25	Gy Fr	Yes	No	Grogginess	None	None
4	60	Male	Pancreatic Head Cancer	Primary Lesion (CRT)	50 25	Gy Fr	Yes	No	Epigastric Pain	Atrial Fibrillation Internal Carotid Artery Stenosis	Apixaban Clopidogrel
5	30	Female	Cervical Cancer, Recurrence	Pelvis ParaAo	60 30	Gy Fr	Yes	Somewhat	Epigastric Pain	Pelvic Venous Thrombosis	Edoxaban →cessation
6	80	Male	Hepatocellular Cancer	Liver S5	48 8	Gy Fr	No	Yes	Melena	Cirrhosis	None
7	60	Female	Endometrial Cancer, Recurrence	Pelvis ParaAo	60 30	Gy Fr	No	Yes	Vomiting	Cirrhosis after Mitral Valve Replacement	Warfarin

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).

## 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 ther-

apy, 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-

**Table 2.**

No.	Age (by 10 Years)	Sex	Underlying Disease	PPI (before Onset)	Original Alb (g/dL)	Alb (g/dL)	Original Hb (g/dL)	Hb (g/dL)	Total Blood Transfusion Volume (units)	Onset (after Irradiation)	Hemostasis	Course	Course (after Onset)
1	70	Female	Endometrial Cancer, Recurrence	none	4.0	3.8	11.0	7.2	70	3	months	Successful	Hospital Visits for 14 Months Died after 17 Months
2	80	Male	Ureteral Cancer	none	3.8	3.5	12.5	5.6	10	3	months	Natural Hemostasis	Hospital Visits for 6 Months Alive after 8 Months
3	70	Male	Biliary Cancer	Vonoprazan 10mg, from before RT	2.4	2.3	11.3	3.5	46	5	months	Uncontrollable →surgery	Hospital Visits for 6 Months Died after 8 Months
4	60	Male	Pancreatic Head Cancer	Vonoprazan 10mg, 30 Days	3.9	2.5	11.8	5.7	42	3	months	Successful →rebleeding →re-hemostasis	Outpatient Chemotherapy for 3 Months Died after 8 Months
5	30	Female	Cervical Cancer, Recurrence	Lansoprazole 15mg, 10 Days	3.4	2.8	8.0	4.1	34	4	months	Successful →rebleeding →re-hemostasis	Home-bound for 2 Months Died after 5 Months
6	80	Male	Hepatocellular Cancer	Esomeprazole 10mg, from before RT	3.3	2.7	11.0	6.9	32	3	months	Complication of Endoscopic Treatment	Inpatient Treatment Died after 2 Months
7	60	Female	Endometrial Cancer, Recurrence	none	4.1	2.9	11.8	3.5	76	3	months	Uncontrollable	Inpatient Treatment Died after 9 Months

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 para-aortic 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 widely 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.

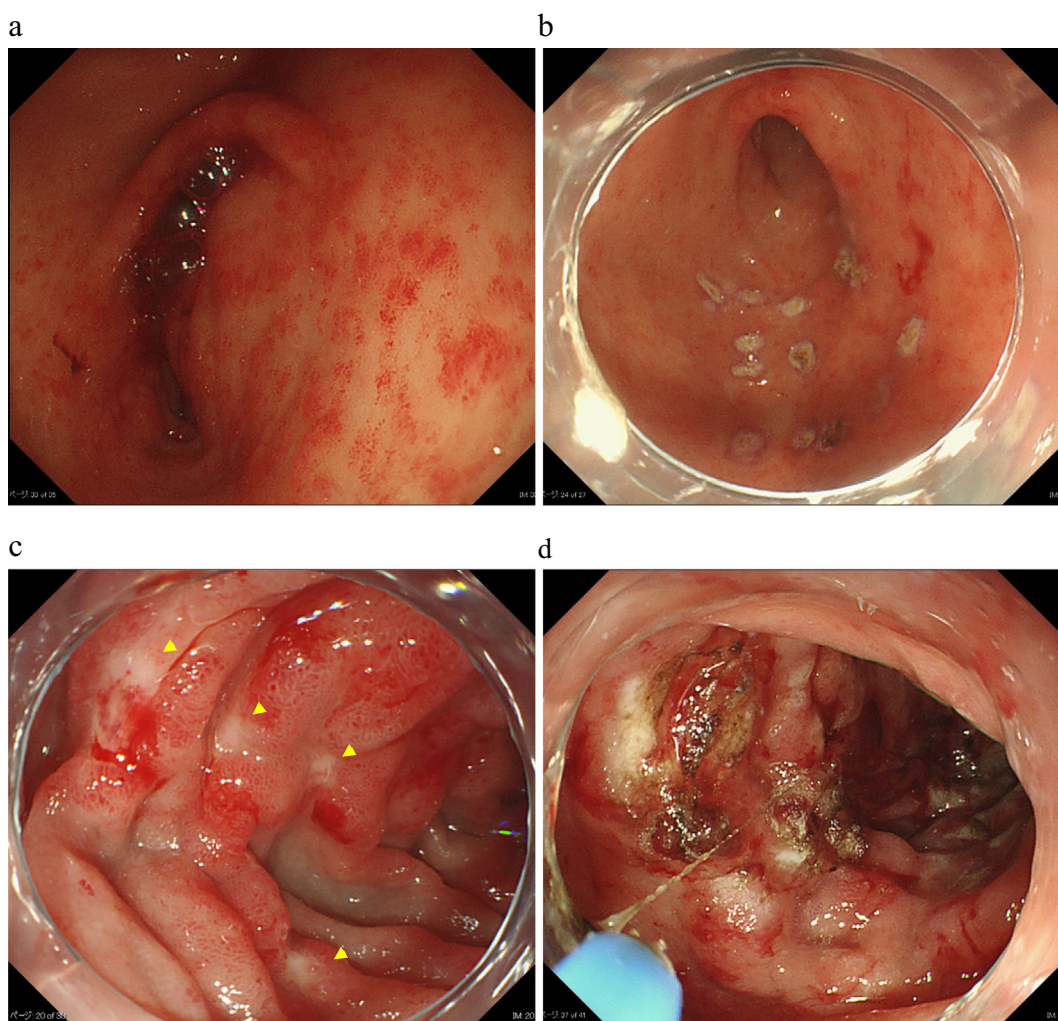
Case 2 (no. 6, Fig. 2): a man in his 80s complained chiefly of melena. He had undergone radiation therapy (48 Gy/8 fr) for hepatocellular carcinoma (S5). Approximately 3 months later, melena was observed, and he was medically examined. His Hb level decreased from 11.0 g/dL to 6.9 g/dL. He had a medical 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 from 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

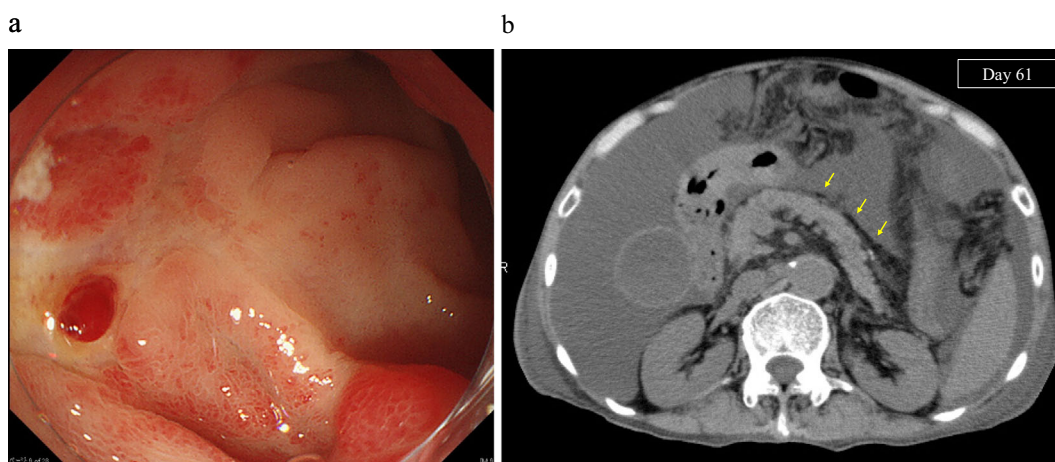
To the best of our knowledge, the present paper is the first report to summarize clinical cases of radiation-induced hemorrhagic gastroduodenitis. The results of the present study indicate that actively attempting hemostasis through APC and surgery to treat radiation-induced hemorrhagic gastroduodenitis 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



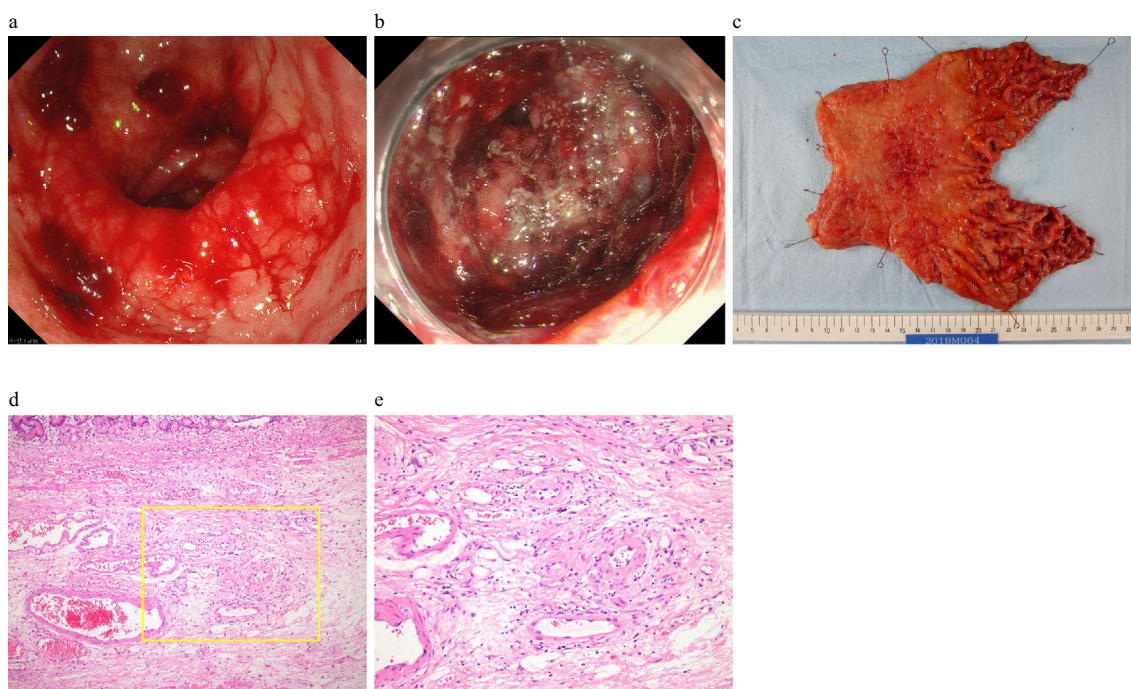
**Figure 1.** Recurring hemorrhaging associated with radiation-induced hemorrhagic gastroduodenitis. **a:** Esophagogastroduodenoscopy: red hemorrhagic mucous membrane in a fragile condition was found from the antrum to the pyloric antrum. **b:** Esophagogastroduodenoscopy: while performing APC for the lesion in “a,” oozing from part of the red mucous membrane was confirmed. **c:** Esophagogastroduodenoscopy: a red hemorrhagic mucous membrane in a fragile condition was found in a wide area of the descending part of the duodenum. There was also a small ulcer noted following APC (arrow). Oozing from the part of the red mucous membrane was noted. **d:** Esophagogastroduodenoscopy: while conducting APC to treat the lesion in “c,” a portion of the red mucous membrane was found to exhibit oozing.

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 he-

patocellular 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



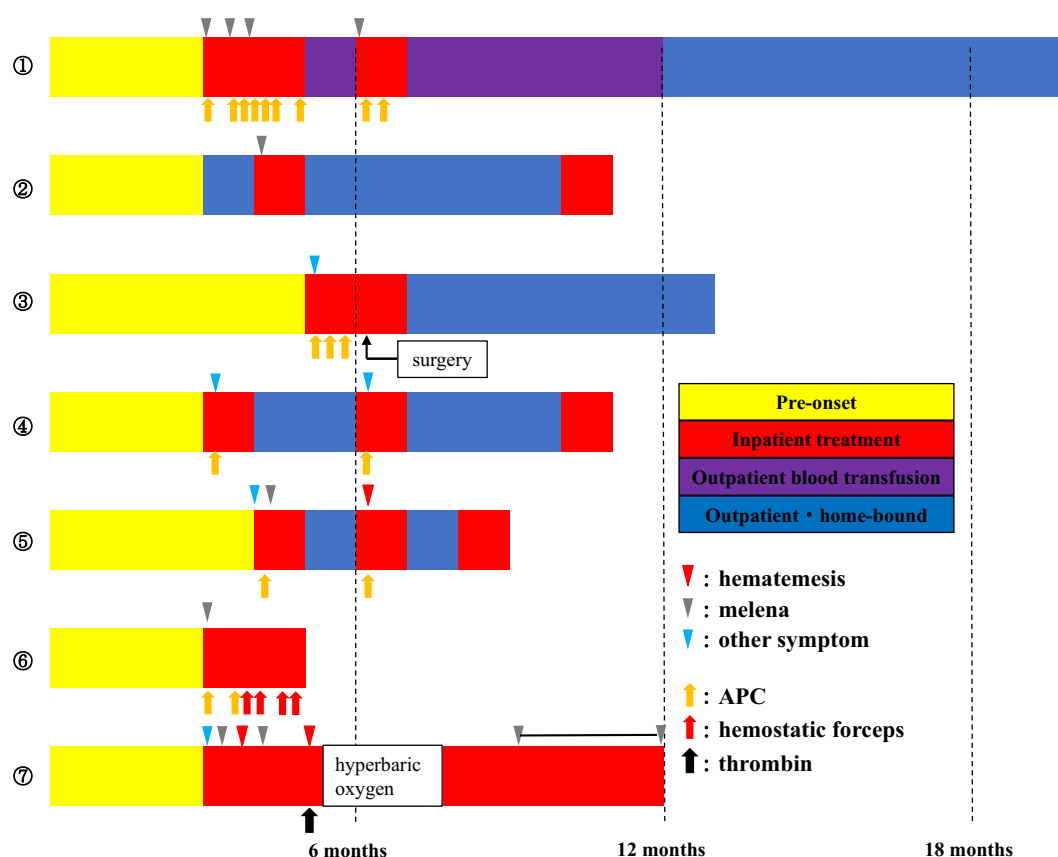
**Figure 2.** Complication of endoscopic hemostasis. a: Esophagogastroduodenoscopy: upper gastrointestinal endoscopy confirmed a red edematous mucous membrane in a fragile condition below the duodenum bulb together with an ulcer with exposed blood vessels in the superior duodenal angle. b: A computed tomography scan from the 61st day of illness: pneumoretroperitoneum (arrow) and a large volume of ascites were confirmed.



**Figure 3.** Surgical case. a: Esophagogastroduodenoscopy: a red hemorrhagic mucous membrane in a fragile condition was found widely ranging from the antrum to the pyloric antrum. b: Esophagogastroduodenoscopy: APC confirmed recurring hemorrhaging despite multiple attempts at hemostasis. c: Excised specimen. d: Histopathological findings: mild fibrous thickening was confirmed in submucosal small blood vessels. e: Histopathological findings: high-power enlargement of mild fibrous thickening.

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 re-

ported. 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-



**Figure 4.** 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.

tion duodenitis by suppressing repair of the epithelium via inhibition of the vascular endothelial growth factor receptor and tyrosine kinase (23). As such, no consensus has been reached about molecular targeted therapy. The present study was limited by the fact that it was a single-center retrospective study with a small sample size.

### Conclusions

Actively attempting hemostasis through APC and surgery to treat radiation-induced hemorrhagic gastroduodenitis is effective. Because antithrombotic agents pose a risk of hemorrhaging, hemostasis should therefore be achieved with repeated APC.

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

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### References

- Denton AS, Andreyev HJN, Forbes A, Maher EJ. Systematic review for non-surgical interventions for the management of late radiation proctitis. *Br J Cancer* **87**: 134-143, 2002.
- Theis VS, Sripadam R, Ramani V, Lal S. Chronic radiation enteritis. *Clin Oncol* **22**: 70-83, 2010.
- Sato Y, Takayama T, Sagawa T, et al. Argon plasma coagulation treatment of hemorrhagic radiation proctopathy: the optimal settings for application and long-term outcome. *Gastrointest Endosc* **73**: 543-549, 2011.
- Shadad AK, Sullivan FJ, Martin JD, Egan LJ. Gastrointestinal radiation injury: symptoms, risk factors and mechanisms. *World J Gastroenterol* **19**: 185-198, 2013.
- Zhu Y, Zhou J, Tao G, et al. Molecular aspects of chronic radiation enteritis. *Clin Invest Med* **34**: E119-E124, 2011.
- Chon YE, Seong J, Kim BK, et al. Gastroduodenal complications after concurrent chemoradiation therapy in patients with hepatocellular carcinoma: endoscopic findings and risk factors. *Int J Radiat Oncol Biol Phys* **81**: 1343-1351, 2011.
- Wada S, Tamada K, Tomiyama T, Yamamoto H, Nakazawa K, Sugano K. Endoscopic hemostasis for radiation-induced gastritis using argon plasma coagulation. *J Gastroenterol Hepatol* **18**: 1215-1218, 2003.
- Corbinais S, Garin L, Pagenault M, Bretagne JF. Successful treatment by argon plasma coagulation of bleeding radiation-induced gastroduodenal vasculopathy. *Endoscopy* **34**: 593, 2002.
- Maekawa S, Aoyama N, Shirasaka D, et al. Argon plasma coagulation for treatment of hemorrhagic radiation gastroduodenitis. *Dig Endosc* **14**: 5-8, 2002.
- Toyoda H, Jaramillo E, Mukai K, et al. Treatment of radiation-induced hemorrhagic duodenitis with argon plasma coagulation. *Endoscopy* **36**: 192, 2004.
- Hashizume H, Sato K, Horiguchi N, et al. A case of hemorrhagic

- gastroduodenitis after proton beam radiation for pancreatic cancer with multiple hemorrhagic risk factors: successful treatment with argon plasma coagulation. *Clin J Gastroenterol* **5**: 336-340, 2012.
12. Kwak HW, Lee WJ, Woo SM, et al. Efficacy of argon plasma coagulation in the treatment of radiation-induced hemorrhagic gastroduodenal vascular ectasia. *Scand J Gastroenterol* **49**: 238-245, 2014.
  13. Liang M, Liwen Z, Juan D, Yun Z, Yanbo D, Jianping C. A case report of endoscopic therapy for radiation-induced hemorrhagic gastritis in patient with recurrent hepatocellular carcinoma. *Medicine* **97**: e13535, 2018.
  14. Tatsis V, Peponi E, Papadopoulos G, Tsekeris P, Fatouros M, Glantzounis G. Subtotal gastrectomy for diffused hemorrhagic gastritis induced by radiation, following liver resection for hilar cholangiocarcinoma. A case report. *Int J Surg Case Rep* **18**: 30-32, 2016.
  15. Flobert C, Cellier C, Landi B, et al. Severe hemorrhagic gastritis of radiation origin. *Gastroenterol Clin Biol* **22**: 232-234, 1998 (in French).
  16. Kernstine KH, Greensmith JE, Johlin FC, et al. Hyperbaric oxygen treatment of hemorrhagic radiation-induced gastritis after esophagectomy. *Ann Thorac Surg* **80**: 1115-1117, 2005.
  17. Banerjee N, Javed A, Deepak D, Pawar M, Chattopadhyay TK. Hyperbaric oxygen therapy: an adjuvant treatment modality for chemo-radiation induced hemorrhagic gastritis. *Trop Gastroenterol* **32**: 248-250, 2011.
  18. Brown C, Subramanian V, Wilcox CM, Peter S. Somatostatin analogues in the treatment of recurrent bleeding from gastrointestinal vascular malformations: an overview and systematic review of prospective observational studies. *Dig Dis Sci* **55**: 2129-2134, 2010.
  19. Yun HG, Kim HY, Kim DY, Lim YJ. Successful treatment of intractable bleeding caused by radiation-induced hemorrhagic gastritis using oral prednisolone: a case report. *Cancer Res Treat* **47**: 334-338, 2015.
  20. Zhang L, Xia WJ, Zhang ZS, Lu XL. Growth hormone used to control intractable bleeding caused by radiation-induced gastritis. *World J Gastroenterol* **21**: 9453-9456, 2015.
  21. Maire F, Muller N, Lévy P. First case of radiation-induced diffuse hemorrhagic gastritis successfully treated with intravenous bevacizumab. *Am J Gastroenterol* **112**: 1349-1350, 2017.
  22. Lordick F, Geinitz H, Theisen J, Sendler A, Sarbia M. Increase risk of ischemic bowel complications during treatment with bevacizumab after pelvic irradiation: report of three cases. *Int J Radiat Oncol Biol Phys* **64**: 1295-1298, 2006.
  23. Yanai S, Nakamura S, Oho A, et al. Radiation-induced hemorrhagic duodenitis associated with sorafenib treatment. *Clin J Gastroenterol* **8**: 116-119, 2015.
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