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CASE REPORT Open Access

Second-line therapy for *Helicobacter pylori* eradication causing antibiotic-associated hemorrhagic colitis

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Abstract

Objective: *Helicobacter pylori* (*H. pylori*) eradication rarely develops into antibiotic-associated hemorrhagic colitis (AAHC), in which the etiology of colitis remains unclear. We herein report a rare case of AAHC caused by second-line therapy for *H. pylori* eradication.

Results: A 65-year-old female was administered second-line therapy for *H. pylori* composed of 1500 mg of amoxicillin, 500 mg of metronidazole and 40 mg of vonoprazan for 7 days because of first-line therapy failure. A day after completing second-line therapy, she complained of abdominal pain and hematochezia. Colonoscopy revealed a hemorrhage and edematous mucosa with no transparent vascular pattern in the transverse colon. A bacterial culture detected *Klebsiella oxytoca* (*K. oxytoca*), but no other pathogenic bacteria. A drug-induced lymphocyte stimulation test (DLST) showed positive reactions for both amoxicillin and metronidazole. According to these findings, the patient was diagnosed with AAHC. Bowel rest for 6 days relieved her abdominal pain and hematochezia.

Conclusions: The present case developed AAHC caused by second-line therapy for *H. pylori* eradication. The pathogenesis is considered to be associated with microbial substitution as well as a delayed-type allergy to antibiotics, suggesting that AAHC is a potential adverse event of second-line therapy for *H. pylori* eradication.

Background

Helicobacter pylori (*H. pylori*) infection has been known to cause many gastrointestinal disorders including gastroduodenal ulcers, gastric cancer and lymphoma, and idiopathic thrombocytopenic purpura [1–5]. *H. pylori* eradication is thus recommended to prevent these gastrointestinal disorders [6, 7]. In Japan, treatment for *H. pylori*-associated gastritis is now covered by health insurance [8]. The success rate of first-line therapy for *H. pylori* eradication is considered to be around 70–80% [9]. Second-line therapy for *H. pylori* eradication is needed for the remaining cases. Although *H. pylori* eradication occasionally causes adverse events, such as diarrhea and eruptions, it rarely develops into antibiotic-associated hemorrhagic colitis (AAHC), in which the etiology of colitis remains unclear. We herein report a rare case of AAHC caused by second-line therapy for *H. pylori* eradication.

Case report

A 65-year-old female, who had systemic lupus erythematosus and was taking 5 mg of prednisolone, underwent gastric mucosal resection to remove gastric adenoma. The endoscopic findings of chronic gastritis were confirmed. Histological findings and culture of the gastric specimens obtained from the gastric antrum and body by an endoscopic biopsy procedure detected an *H. pylori* infection. She was therefore administered first-line therapy composed of 1500 mg of amoxicillin, 800 mg of clarithromycin and 60 mg of lansoprazole for 7 days to eradicate *H. pylori* in December 2014. A urea breath test was performed to assess the effect of the

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eradication and revealed a positive result for *H. pylori* infection. Seven months after the first-line therapy, the patient was prescribed second-line therapy composed of 1500 mg of amoxicillin, 500 mg of metronidazole and 40 mg of vonoprazan for 7 days to eradicate *H. pylori* in July 2015. A day after completing second-line therapy, she complained of abdominal pain and hematochezia. Blood tests showed increases in neutrophil (6090/μL) and C-reactive protein (1.38 μg/mL) levels, whereas the hemoglobin level was within the normal limits. Colonoscopy revealed a hemorrhage and edematous mucosa with no transparent vascular pattern in the transverse colon (Fig. 1). Histological findings of the biopsy specimens obtained from the transverse colon showed severe infiltrations of neutrophil and lymphocytes and a hemorrhage in the lamina propria (Fig. 2). A bacterial culture detected *Klebsiella oxytoca* (*K. oxytoca*), but not *Clostridium difficile* or other pathogenic bacteria. A drug-induced lymphocyte stimulation test (DLST) showed positive reactions for both amoxicillin and metronidazole. According to these findings, the patient was diagnosed with AAHC.

Bowel rest for 6 days under the oral administration of 5 mg of prednisolone relieved her abdominal pain and hematochezia. Typical symptoms due to SLE have been relieved for 20 months with conservative treatment alone, and no vasculitis was histologically detected in biopsy specimens of the colon. Therefore, lupus enteritis was not thought to be associated with the pathogenesis of the enteric disorder in the patient.

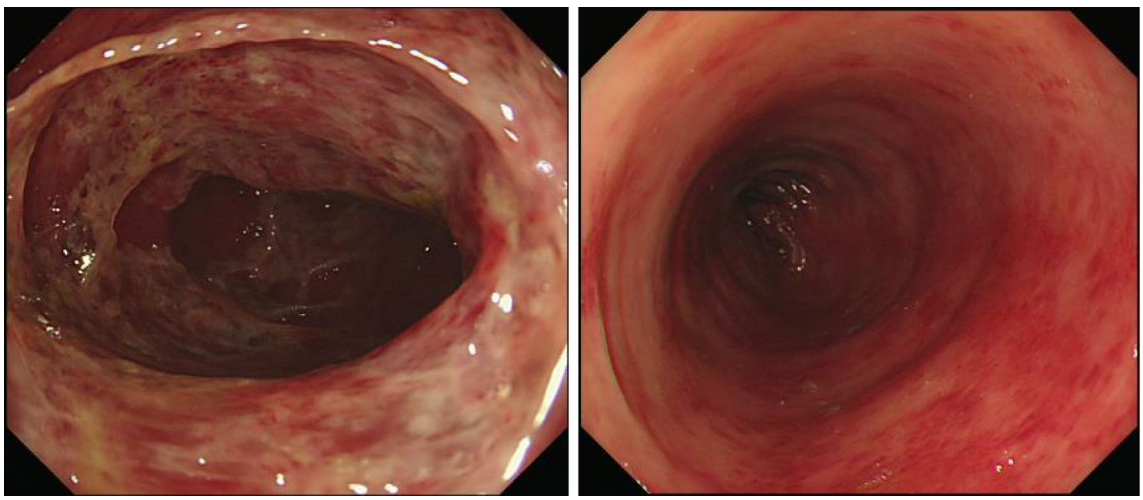

Fig. 1 Colonoscopy findings. Diffusely edematous mucosa with mucus, a hemorrhage and no transparent vascular pattern was detected in the transverse colon

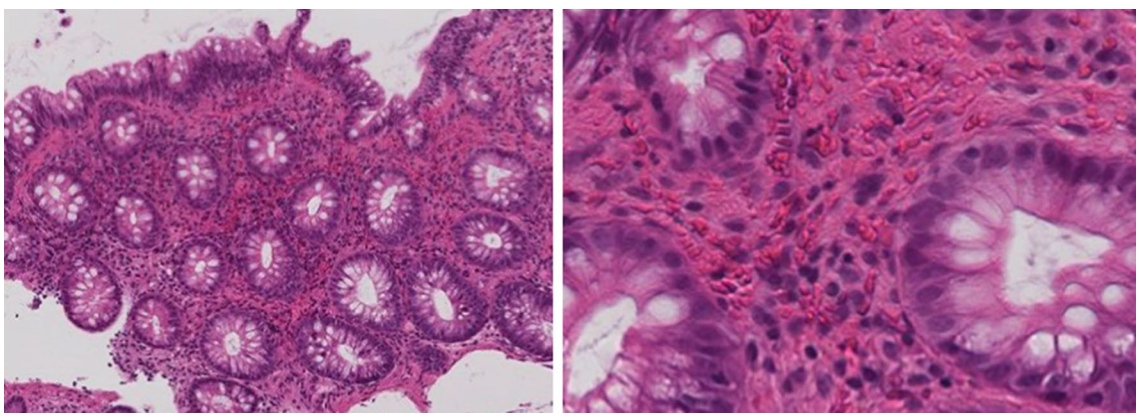

Fig. 2 Histological findings. Severe infiltrations of neutrophil and lymphocytes and a hemorrhage in the lamina propria were detected in the biopsy specimens obtained from the transverse colon (magnifications: 100/400)

Discussion

We herein report a rare case of AAHC that developed after the completion of second-line therapy using amoxicillin, metronidazole and vonoprazan for *H. pylori* eradication. Clinicians must pay careful attention to the possibility of this disorder, even when no side effects develop after the first-line therapy for *H. pylori* eradication.

While the incidence rate of AAHC after the first-line therapy for *H. pylori* eradication has been reported to range from 0.35 to 0.6% [10, 11], the frequency of AAHC after second-line therapy for *H. pylori* eradication is still unclear. A total of five previous cases that exhibited AAHC after completing second-line therapy for *H. pylori* eradication were identified in a literature search on the PubMed and Ichushi databases (Table 1) [12, 13]. Including the present case, there were 2 males and 4 females, and the mean age of the cases was 59.3 years old. Five cases exhibited AAHC after completing second-line *H. pylori* eradication therapy, suggesting that an immediate-type allergy was not a cause of AAHC. In two cases, *K. oxytoca* was isolated from the stool culture. It is known that stool testing reveals *K. oxytoca* in significant amounts in the majority of patients with AAHC [14]. *K. oxytoca* strains isolated from patients with AAHC are known to produce a cytotoxin, which were shown to cause cell death in cultured Hep2, Vero, CHOK1, and HeLa cell lines as well as in an isolated intestinal loop rabbit model [15, 16]. These studies indicated that microbial substitution by amoxicillin- and/or metronidazole-induced overgrowth of *K. oxytoca* could be associated with the development of AAHC in patients with the administration of second-line therapy for *H. pylori* eradication. The DLST was performed only in our case, which detected positive reactions for amoxicillin and metronidazole. Collectively, two mechanisms are thought to be involved in the pathogenesis of AAHC. First, microbial alterations accumulate by repeated antibiotic administration, thereby leading to AAHC at the second-line treatment. Second, amoxicillin sensitization may have been acquired at the time of first-line therapy, and a delayed allergic reaction may have occurred at the time of second-line therapy. Although the delayed-type allergy was a potential cause of AAHC in our case, it is unclear whether this type of allergy is a major cause of AAHC in patients receiving second-line therapy for *H. pylori* eradication. A greater accumulation of cases is warranted to understand the etiology of AAHC due to second-line therapy for *H. pylori* eradication.

Conclusions

In summary, we herein reported a rare case of AAHC caused by second-line therapy for *H. pylori* eradication. Due to the detection of *K. oxytoca* and positive reaction on the DLST for amoxicillin and metronidazole, the pathogenesis of the present case was considered to be associated with microbial substitution as well as a

Table 1 Reported cases of antibiotic-associated hemorrhagic colitis due to the second-line therapy for Helicobacter pylori eradication

Age	Gender	Symptoms	Onset	First-line therapy	Second-line therapy	Fecal bacterial culture	DLST	References
58	F	Abdominal pain, bloody diarrhea	8 days after starting eradication	CAM + AMPC + RPZ	MNZ 500 mg + AMPC 1500 mg + RPZ 20 mg	Pathogenic bacteria was not detected	Not described	#12
54	M	Abdominal pain, bloody diarrhea	7 days after starting eradication	CAM + AMPC + RPZ	MNZ 500 mg + AMPC 1500 mg + RPZ 20 mg	Pathogenic bacteria was not detected	Not described	#12
59	F	Abdominal pain, bloody diarrhea	9 days after starting eradication	CAM + AMPC + RPZ	MNZ 500 mg + AMPC 1500 mg + RPZ 20 mg	Pathogenic bacteria was not detected	Not described	#12
60	F	Abdominal pain, bloody diarrhea	9 days after starting eradication	CAM + AMPC + PPI	MNZ + AMPC + PPI	*Klebsiella oxytoca*	Not described	#13
50	M	Abdominal pain, hematochezia	6 days after starting eradication	CAM + AMPC + PPI	MNZ + AMPC + PPI	Not described	Not described	#13
65	F	Abdominal pain, hematochezia	8 days after starting eradication	CAM 800 mg + AMPC 1500 mg + LPZ 60 mg	MNZ 500 mg + AMPC 1500 mg + Vonoprazan 40 mg	*Klebsiella oxytoca*	Positive for both AMPC and MNZ	Present case

CAM clarithromycin, *AMPC* amoxicillin, *MNZ* metronidazole, *RPZ* rabeprazole, *LPZ* lansoprazole, *PPI* proton pump inhibitor

delayed-type allergy to amoxicillin and/or metronidazole. Clinicians must pay careful attention to the possibility of AAHC, even when administering second-line therapy for *H. pylori* eradication.

Abbreviations
H. pylori: *Helicobacter pylori*; AAHC: antibiotic-associated hemorrhagic colitis; *K. oxytoca*: *Klebsiella oxytoca*; DLST: drug-induced lymphocyte stimulation test; CAM: clarithromycin; AMPC: amoxicillin; MNZ: metronidazole; RPZ: rabeprazole; LPZ: lansoprazole; PPI: proton pump inhibitor.

Authors' contributions
KT and MF contributed equally to this study. KT and MF conceived the report, collected data, and wrote the first draft of the report. KT, AS and YN followed up the patient. SF, NU and SK performed endoscopy and evaluated the disease severity. TG and JS evaluated radiological images including computed tomography. KM and TO supervised the study. All authors contributed to the critical revision of the report for important intellectual content. All authors read and approved the final manuscript.

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Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Consent for publication
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Ethics approval and consent to participate
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References

1. Marshall BJ. *Helicobacter pylori*. Am J Gastroenterol. 1994;89:S116–28.
2. Malfertheiner P, Leodolter A, Peitz U. Cure of *Helicobacter pylori*—associated ulcer disease through eradication. Baillieres Best Pract Res Clin Gastroenterol. 2000;14:119–32.
3. Uemura N, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, et al. *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med. 2001;345:784–9.
4. Walt RP. Regression of MALT lymphoma and treatment for *Helicobacter pylori*. Lancet. 1996;348:1041–2.
5. Choe YH, Kim SK, Son BK, Lee DH, Hong YC, Pai SH. Randomized placebo-controlled trial of *Helicobacter pylori* eradication for iron- deficiency anemia in preadolescent children and adolescents. Helicobacter. 1999;4:135–9.
6. Gisbert JP, Khorrami S, Carballo F, Calvet X, Gene E, Dominguez-Muñoz E. *Helicobacter pylori* eradication therapy vs. antisecretory non-eradication therapy (with or without long-term maintenance antisecretory therapy) for the prevention of recurrent bleeding from peptic ulcer. Cochrane Database Syst Rev. 2004;2:004062.
7. Fukase K, Kato M, Kikuchi S. Eradication of *Helicobacter pylori* after endoscopic resection of early gastric cancer reduced the incidence of metachronous gastric cancer. Lancet. 2008;372:392–7.
8. Asaka M, Takahashi S, et al. Guidelines for the management of *Helicobacter pylori* infection in Japan: 2009 revised edition. Helicobacter. 2010;15:1–20.
9. Laheij RJ, Rossum LG, Jansen JB, Straatman H, Verbeek AL. Evaluation of treatment regimens to cure *Helicobacter pylori* infection—a meta-analysis. Aliment Pharmacol Ther. 1999;13:857–64.
10. Ishikawa S, Hayami Y, Sugawara K, Tanaka T, Yamamoto N, Hashimoto M, et al. A study on 19 cases of antibiotic-associated hemorrhagic colitis. Progr Dig Endosc. 1998;53:132–3.
11. Kashihara W, Hashimoto A, Kou H, Kin Y, Nishitani H, Okui M, Fukui S, et al. Case of antibiotic-associated hemorrhagic colitis during eradication therapy for *Helicobacter pylori*. Helicobacter Res. 1998;2:580–1.
12. Ikegami R, Kamiya K, Iwashige H. Three cases of antibiotic-associated hemorrhagic colitis after second-line therapy for *Helicobacter pylori*. J Jpn Soc Coloproctol. 2015;68:419–24.
13. Kakinoki K. Two cases of antibiotic-associated hemorrhagic colitis after second-line therapy for *Helicobacter pylori*. J Jpn Assoc Infect Dis. 2015;89:247.
14. Zollner-Schwetz I, Hogenauer C, Joainig M, Weberhofer P, Gorkiewicz G, Valentin T, et al. Role of *Klebsiella oxytoca* in antibiotic-associated diarrhea. Clin Infect Dis. 2008;47:e74–8.
15. Higaki M, Chida T, Takano H, Nakaya R. Cytotoxic component(s) of *Klebsiella oxytoca* on HEp-2 cells. Microbiol Immunol. 1990;34:147–51.
16. Minami J, Katayama S, Matsushita O, Sakamoto H, Okabe A. Enterotoxic activity of *Klebsiella oxytoca* cytotoxin in rabbit intestinal loops. Infect Immun. 1994;62:172–7.