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CASE REPORT

Hepatic portal venous gas associated with *Klebsiella oxytoca* infection in the absence of preceding antibiotic treatment

Hidekazu Tanaka[1] · Tomohiro Watanabe[1] · Tomoyuki Nagai[1] · Kosuke Minaga[1] · Ken Kamata[1] · Yoriaki Komeda[1] · Masatoshi Kudo[1]

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Abstract
Klebsiella oxytoca (*K. oxytoca*) is a causative organism for hemorrhagic antibiotic-associated colitis. *K. oxytoca* infection is a typical example of microbial substitution diseases caused by exposure to antibiotics prior to the onset of diarrhea. Here, we repot a case with ileitis associated with *K. oxytoca* infection in the absence of preceding antibiotic treatment. Interestingly, abdominal computed tomography revealed wall thickening of the ileum and hepatic portal venous gas (HPVG). *K. oxytoca* was isolated from the stool. This very elderly patient had been treated with azathioprine for long-standing history of ulcerative colitis. Immuno-compromised state of this patient was considered to allow overgrowth of *K. oxytoca* in the small bowel to cause not only ileitis but also HPVG.

Keywords Hepatic portal venous gas · Antibiotics · *Klebsiella oxytoca*

Introduction

Klebsiella oxytoca (K. oxytoca) is a Gram-negative bacterium ubiquitously present in the soil and water [1]. This bacterium is a resident of the gut in a significant population of healthy individuals and considered as a constituent of the normal intestinal microflora [2]. It should be noted that *K. oxytoca* constitutively expresses β-lactamases conferring resistance to penicillin [1] and that antibiotic treatment sometimes results in colonic overgrowth of *K. oxytoca* leading to the development of hemorrhagic colitis [3]. Thus, preceding antibiotic treatment is a prerequisite for the conversion of *K. oxytoca* from a commensal symbiont to a pathobiont with the ability to induce hemorrhagic colitis. Now it is generally accepted that *K. oxytoca* is a causative organism of hemorrhagic antibiotic-associated colitis [4].

Hepatic portal venous gas (HPVG) is associated with life-threatening abdominal diseases [5]. Survival and prognosis of patients exhibiting HPVG depend upon the underlying etiologies. More than 70% cases with HPVG are associated with bowel necrosis, which explains the high mortality rate [5, 6]. Thus, we need to consider the possibility of urgent surgical intervention upon encounter with patients exhibiting HPVG [7]. Here we present a case exhibiting HPVG on computed tomography (CT). Surprisingly, the development of HPVG in this case was associated with *K. oxytoca* infection in the absence of preceding antibiotic treatment.

Case report

An 87-year-old female with a past history of ulcerative colitis (UC) was admitted to the hospital for watery diarrhea, abdominal pain and vomiting. She was diagnosed as UC at 65 year old and then treated with 5-aminosalicylic acid (2400 mg/day) and azathioprine (100 mg/day). Physical examination revealed normal blood pressure (132/64 mmHg) with tachycardia (96 /min) and normal body temperature. The abdomen was tender without any sign of peritoneal inflammation. Blood examinations on admission revealed mild elevation of serum level of C-reactive protein (CRP) accompanied by leukocytosis and thrombocytosis (Table 1). Mild anemia probably caused by azathioprine was also seen. Coagulation tests, renal function tests and liver function tests were normal. 2 days after the admission, her serum level of CRP was markedly increased up to 10.2 mg/dL (Table 1).

✉ Tomohiro Watanabe
tomohiro@med.kindai.ac.jp

[1] Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan

Table 1 Laboratory data

	Day 0	Day 2
WBC ($\times 10^3/\mu L$)	10.23	8.48
RBC ($\times 10^6/\mu L$)	2.89	2.79
Hb (g/dL)	10.5	10.1
Ht (%)	31.0	29.7
Plt ($\times 10^4/\mu L$)	48.2	47.1
PT (%)	103.4	92.9
APTT (s)	25.9	Not examined
D-dimer (μg/mL)	0.9	Not examined
FDP (μg/mL)	3.7	5.5
CRP (mg/dL)	0.136	10.200
TP (g/dL)	5.8	5.6
Albumin (g/dL)	3.6	3.1
T-Bil (mg/dL)	0.6	0.7
AST (U/L)	17	16
ALT (U/L)	8	7
LDH (U/L)	181	190
CPK (U/L)	161	61
γ-GTP (U/L)	8	8
Amy (U/L)	55	40
BUN (mg/dL)	15	26
Cr (mg/dL)	0.73	0.96
Na (mmol/L)	139	138
K (mmol/L)	4.9	4.7
Cl (mmol/L)	104	101

These results of physical and blood examinations suggested the presence of viral or bacterial enterocolitis.

CT was performed to determine the sites of inflammation in the gastrointestinal tract on admission. Wall thickening of the ileum was seen in contrast-enhanced CT, suggesting the presence of ileitis (Fig. 1a). Accumulation of gas in the left lobe of the liver was seen (Fig. 1b). Accumulation of the gas was distributed in the peripheral sites of the left lobe (Fig. 1b). The presence of gas was not detected in the bowel wall or in the extra-hepatic portal vein. This peripheral gas distribution was fully consistent with that of HPVG. The presence of bowel ischemia or necrosis was unlikely since formation of closed-loop obstruction, bowel wall hypo-enhancement, colon decompression, or ascites was not detected on CT [8, 9]. Moreover, exacerbation of UC was also unlikely since no abnormal findings were seen on her entire colon on CT. Based on these findings, she was diagnosed as ileitis accompanying HVPG due to gas-producing bacteria and then treated with Flomoxef (1.0 g/day).

Intravenous fluid and antibiotics therapy improved her symptoms. Both HPVG and the wall thickening of the ileum disappeared on CT 4 days after the admission. Moreover, her serum level of CRP was markedly decreased (1.3 mg/dL) 7 days after admission. *K. oxytoca* was isolated from her stool obtained on admission, whereas no other pathogenic bacteria including *Clostridium difficile* were isolated from her stool or blood. The bacterial burden of *K. oxytoca* was not so high since less than 10,000 colonies of this bacterium were detected in her feces. She had not been treated with antibiotics before admission. Colonoscopy was performed 6 days after admission. Mucosal appearance at colonoscopy revealed a partial loss of normal vascular patterns and ulcer scars in the transverse colon and rectum corresponding to mild disease activity and score 1 in Mayo score of endoscopic severity of disease. The terminal ileum was intact. She was finally diagnosed as *K. oxytoca*-associated ileitis exhibiting HVPG in the absence of preceding antibiotic treatment.

Discussion

K. oxytoca is a causative agent of hemorrhagic antibiotic-associated colitis [4]. β-lactamases constitutively expressed by *K. oxytoca* confer resistance to penicillin and thereby induce colonic overgrowth of this bacterium after antibiotic treatment [1]. Such overgrowth of *K. oxytoca* mediates the development of hemorrhagic colitis through the production of cytotoxins [4]. Thus, preceding antibiotic treatment converts the bacterial property of *K. oxytoca* from a commensal symbiont to a pathobiont with the ability to induce hemorrhagic colitis. It is now generally accepted that hemorrhagic colitis due to *K. oxytoca* infection is a typical example of microbial substitution diseases in parallel to pseudomembranous colitis due to *Clostridium difficile* infection (CDI) [10]. Here, we report a case with ileitis associated with *K. oxytoca* infection in the absence of exposure to antibiotics prior to the onset of diarrhea. This case is unique in that *K. oxytoca* exerts its pathogenicity in the absence of antibiotic treatment and thus ileitis due to *K. oxytoca* infection did not occur as a microbial substitution phenomenon.

One question arising from this case is the mechanisms accounting for the development of pathogenic *K. oxytoca* infection without the exposure to antibiotics. In this regard, this very elderly (87 years old) patient was treated with azathioprine, an immunomodulator, for UC. Thus, this patient was considered as an immuno-compromised host. Therefore, it is likely that the immuno-suppressive state might allow overgrowth of *K. oxytoca* even in the absence of exposure to antibiotics. In line with this idea, recent animal studies show that colonic expansion of *K. oxytoca* associated with cancer cachexia, another type of the immuno-compromised state, plays pathogenic roles through impairment of gut barrier function [11].

HPVG is caused by various gastrointestinal disorders [5]. As for the pathogenesis of HPVG, two mechanisms have been proposed [7]. First mechanism is that elevated

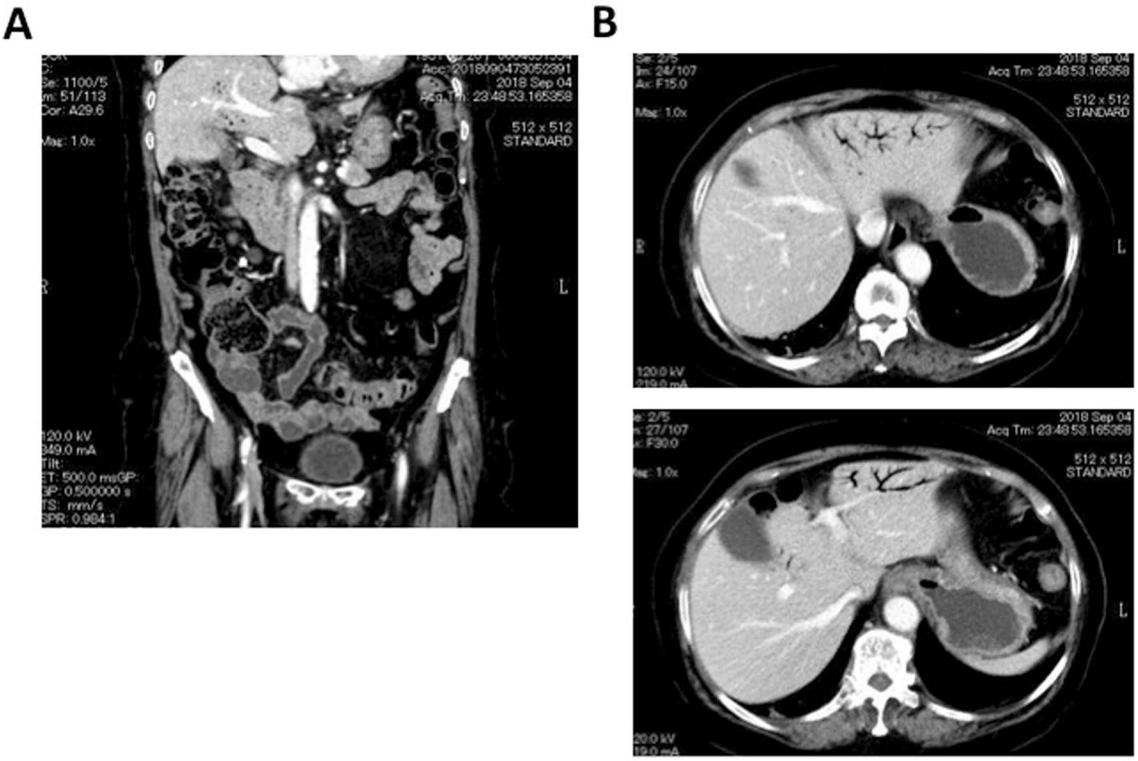

Fig. 1 Abdominal computed tomography on admission. Wall thickening of the ileum (**a**) and accumulation of peripheral gas in the left lobe of the liver (**b**) were seen in the contrast-enhanced computed tomography. Distribution pattern of gas was consistent with that of hepatic portal venous gas

intramural pressure by bowel distension leads to the entrance of intraluminal gas into the venous circulation in the damaged intestinal mucosa. Second mechanism is that gas-producing bacteria invade into the submucosa and then enter into the portal venous system [7]. Given the fact that no findings highly suggestive of bowel obstruction or ischemia were detected on CT, translocation of gas-producing bacteria into the portal circulation was considered to be a primary mechanism for the development of HPVG in this case. In this regard, a H_2 gas-producing *K. oxytoca* strain was isolated from a hot spring [12, 13]. Moreover, a case of air-filled liver abscess caused by *K. oxytoca* infection was also reported [14]. Thus, it is possible that infection with certain *K. oxytoca* strain with the ability to produce gas may be involved in the development of HPVG in this case. Confirmation of this idea awaits future studies addressing the ability to produce gas and cytotoxins in *K. oxytoca* strains isolated from the blood and stool in patients.

We need to maintain a high index of suspicion for CDI in UC since the incidence of CDI is increasing in UC patients [15, 16]. Moreover, CDI can occur in UC patients even in the absence of prior antibiotic use [15]. Thus, exclusion of CDI is recommended in UC patients presenting watery diarrhea although *Clostridium difficile* was not detected in stool culture in this case. Detection of CD toxins in the feces is very useful for rapid diagnosis of CDI [15, 16].

Different from a typical case with hemorrhagic antibiotic-associated colitis due to *K. oxytoca* infection, this patient did not manifest bloody stool in her clinical course. Such lack of hemorrhage raises the possibility that detection of *K. oxytoca* from the feces means isolation of the patient's commensal bacterium rather than the pathogenic bacterium. In addition, *K. oxytoca* had not been isolated from the blood in this case. Thus, we need to be cautious regarding the interpretation of pathogenicity of *K. oxytoca* in this case. However, it is also possible that lack of hemorrhage does not necessarily exclude *K. oxytoca* infection since clinical manifestations or pathogenic roles played by this bacterium have been poorly defined in the absence of preceding antibiotic treatment. Although both bacterial and host factors are involved in the conversion of *K. oxytoca* from a commensal symbiont to a pathobiont [1], the preceding antibiotic treatment has been identified as the only host factor for this conversion [4]. Whether the immuno-compromised state can be regarded as another risk factor in addition to the antibiotic treatment requires further accumulation of cases with *K. oxytoca* infection in the immuno-compromised hosts.

In conclusion, we report a case with *K. oxytoca* infection in the absence of exposure to antibiotics prior to the onset of diarrhea. Translocation of gas-producing *K. oxytoca* into the portal circulation might be involved in the development of HPVG in this case. We need to bear in mind a possibility of *K. oxytoca* infection in an immuno-compromised host even in the absence of preceding antibiotic therapy.

Compliance with ethical standards

Conflict of interest Hidekazu Tanaka, Tomohiro Watanabe, Tomoyuki Nagai, Kosuke Minaga, Ken Kamata, Yoriaki Komeda, and Masatoshi Kudo declare that they have no conflict of interest in the subject matter or materials discussed in the manuscript.

Human rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all patients for being included in the study.

References

1. Joainig MM, Gorkiewicz G, Leitner E, et al. Cytotoxic effects of *Klebsiella oxytoca* strains isolated from patients with antibiotic-associated hemorrhagic colitis or other diseases caused by infections and from healthy subjects. J Clin Microbiol. 2010;48:817–24.
2. Schneditz G, Rentner J, Roier S, et al. Enterotoxicity of a nonribosomal peptide causes antibiotic-associated colitis. Proc Natl Acad Sci USA. 2014;111:13181–6.
3. Zollner-Schwetz I, Hogenauer C, Joainig M, et al. Role of *Klebsiella oxytoca* in antibiotic-associated diarrhea. Clin Infect Dis. 2008;47:e74-8.
4. Hogenauer C, Langner C, Beubler E, et al. *Klebsiella oxytoca* as a causative organism of antibiotic-associated hemorrhagic colitis. N Engl J Med. 2006;355:2418–26.
5. Abboud B, El Hachem J, Yazbeck T, et al. Hepatic portal venous gas: physiopathology, etiology, prognosis and treatment. World J Gastroenterol. 2009;15:3585–90.
6. Liebman PR, Patten MT, Manny J, et al. Hepatic–portal venous gas in adults: etiology, pathophysiology and clinical significance. Ann Surg. 1978;187:281–7.
7. Chan SC, Wan YL, Cheung YC, et al. Computed tomography findings in fatal cases of enormous hepatic portal venous gas. World J Gastroenterol. 2005;11:2953–5.
8. Fulwadhva UP, Wortman JR, Sodickson AD. Use of dual-energy CT and iodine maps in evaluation of bowel disease. Radiographics. 2016;36:393–406.
9. Scrima A, Lubner MG, King S, et al. Value of MDCT and clinical and laboratory data for predicting the need for surgical intervention in suspected small-bowel obstruction. AJR Am J Roentgenol. 2017;208:785–93.
10. Dicks LMT, Mikkelsen LS, Brandsborg E, et al. *Clostridium difficile*, the difficult "Kloster" fuelled by antibiotics. Curr Microbiol. 2018. https://doi.org/10.1007/s00284-018-1543-8.
11. Potgens SA, Brossel H, Sboarina M, et al. Klebsiella oxytoca expands in cancer cachexia and acts as a gut pathobiont contributing to intestinal dysfunction. Sci Rep. 2018;8:12321.
12. Minnan L, Jinli H, Xiaobin W, et al. Isolation and characterization of a high H2-producing strain *Klebsiella oxytoca* HP1 from a hot spring. Res Microbiol. 2005;156:76–81.
13. Wu X, Li Q, Dieudonne M, et al. Enhanced H2 gas production from bagasse using adhE inactivated *Klebsiella oxytoca* HP1 by sequential dark-photo fermentations. Bioresour Technol. 2010;101:9605–11.
14. Paasch C, Wilczek S, Strik MW. Liver abscess and sepsis caused by *Clostridium perfringens* and *Klebsiella oxytoca*. Int J Surg Case Rep. 2017;41:180–3.
15. Bossuyt P, Verhaegen J, Van Assche G, et al. Increasing incidence of *Clostridium difficile*-associated diarrhea in inflammatory bowel disease. J Crohns Colitis. 2009;3:4–7.
16. Rodemann JF, Dubberke ER, Reske KA, et al. Incidence of *Clostridium difficile* infection in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2007;5:339–44.