Clinical Journal of Gastroenterology (2019) 12:325–329
https://doi.org/10.1007/s12328-019-00949-z

CASE REPORT

Community-acquired fulminant colitis caused by binary toxin-producing *Clostridium difficile* in Japan

Noriaki Oguri[1] · Akihito Sakuraba[1] · Hiromu Morikubo[1] · Oki Kikuchi[1] · Taro Sato[1] · Soutaro Tokunaga[1] · Shintaro Minowa[1] · Osamu Ikezaki[1] · Tatsuya Mitsui[1] · Miki Miura[1] · Daisuke Saito[1] · Mari Hayashida[1] · Hideaki Mori[1] · Takako Osaki[2] · Shigeru Kamiya[2] · Mitsutoshi Senoh[3] · Haru Kato[3] · Tadakazu Hisamatsu[1]

Received: 28 December 2018 / Accepted: 31 January 2019 / Published online: 14 February 2019

Abstract

We report a case of community-acquired fulminant colitis caused by *Clostridium difficile* in Japan. A 46-year-old woman was diagnosed with severe infectious enterocolitis and was admitted at another hospital. The stool culture was positive for toxigenic *C. difficile*. Since the patient presented with fulminant *C. difficile* infection (CDI) with toxic megacolon, respiratory insufficiency, and circulatory failure, she was transferred to Kyorin University Hospital for intensive care. Intubation and antibiotic therapy were performed. The general condition improved with conservative treatment, and she was discharged without sequelae. While the recovered isolate was toxin A and B-positive and binary toxin-positive, it was identified as polymerase chain reaction (PCR) ribotype ts0592 and *slpA* sequence type ts0592. The isolate was different from PCR ribotype 027 epidemic in Europe and North America. In Japan, binary toxin-producing strains are rare and have not caused an epidemic to date. Furthermore, there are few data on community-acquired CDI in Japan. In this case, a non-elderly woman with no major risk factors such as antibiotic use, administration of proton pump inhibitor and history of gastrointestinal surgery developed community-acquired fulminant CDI caused by the binary toxin-positive strain, and ICU treatment was required. Further studies focusing on the role of binary toxin-positive *C. difficile* in the severity of community-acquired CDI are necessary.

Keywords *Clostridium* (*Clostridioides*) *difficile* · Binary toxin · Fulminant colitis · PCR ribotype · *SlpA* sequence type

Abbreviations

C. difficile	*Clostridium* (*Clostridioides*) *difficile*
CDI	*Clostridium* (*Clostridioides*) *difficile* infection
PCR	Polymerase chain reaction
slpA	Surface layer protein A gene
CT	Computed tomography
ADP	Adenosine diphosphate
ICU	Intensive care unit

Introduction

Clostridium (*Clostridioides*) *difficile* infection (CDI) is one of the most common healthcare-associated infections, especially among elderly hospitalized patients. Highly virulent polymerase chain reaction (PCR) ribotypes 027 and 078, which produce binary toxin, emerged and prevailed in Europe and North America in the 2000s. These strains are associated with remarkably high morbidity and mortality [1, 2]. Binary toxin is known as the third toxin produced by *C. difficile*, which is neither toxin A nor toxin B. It is composed of two unlinked components, the enzymatic component (CDTa) and binding component (CDTb), and acts as an actin-specific adenosine diphosphate (ADP)-ribosyltransferase, which impairs the structure of the actin cytoskeleton in epithelial cells and induces diarrhea [3]. There is no established theory on the relationship between binary toxin and community-acquired CDI. However, it was reported that patients infected with type 078 were younger and had community-acquired CDI more frequently than those with PCR

✉ Tadakazu Hisamatsu
thisamatsu@ks.kyorin-u.ac.jp

[1] Third Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

[2] Department of Infectious Diseases, Kyorin University School of Medicine, Tokyo, Japan

[3] Department of Bacteriology II, National Institute of Infectious Diseases, Tokyo, Japan

ribotype 027 [4], suggesting that the difference in genotype may affect the clinical significance and epidemiology.

No reports of outbreaks caused by binary toxin-positive strains in Japan were noted, and there have only been a few case reports on such strain, including the first report of the PCR ribotype 027 strain in Japan in 2007 [5]. Herein, we report a case of a non-elderly patient with fulminant community-acquired CDI by a binary toxin-positive strain.

Case report

The patient's clinical course is shown in Fig. 1. A 46-year-old woman with vomiting and diarrhea was brought to another hospital of secondary emergency medical institution. The patient had a history of atypical psychosis and was taking psychotropic drugs and laxative; however, she had no major risk factors such as antibiotic use, administration of proton pump inhibitor and history of gastrointestinal surgery prior to hospitalization. Laboratory data showed high levels of white blood cells (WBC 13300/μl) and C-reactive protein (CRP; 17 mg/dl). She was diagnosed with infectious enterocolitis and cefmetazole administration was started to treat her condition. As toxigenic *C. difficile* was detected on the stool specimen taken at the time of admission to the hospital, she was diagnosed with CDI. However, the patient's general condition worsened, and she experienced respiratory and circulatory failure; thus, she was transferred to Kyorin University Hospital for intensive care.

At the time of admission, the patient had watery diarrhea more than ten times a day and her abdomen was abnormally expanded. Her body temperature was 39 °C, and systolic blood pressure decreased to approximately 80 mmHg. Percutaneous oxygen saturation was 90% with the administration of 10 L of O_2 via a reservoir mask. The blood test revealed excessive inflammation and decreased coagulability, and nutritional status (Table 1). An abdominal radiograph showed dilation of the transverse colon to a diameter of 8 cm, and contrast CT revealed pleural effusion, ascites, and marked intestinal edema of the whole colon (Fig. 2). The stool specimen was positive for toxins A/B of *C. difficile* by enzyme immunoassay (EIA). Fecal culture yielded toxin-producing *C. difficile*. She was diagnosed with fulminant CDI with toxic megacolon.

Table 1 Laboratory data at the first visit to Kyorin University Hospital

Blood count		Serum chemistry	
WBC	18900/μl	Na	131 mmol/l
RBC	354×10^4/μl	K	4.2 mmol/l
Hb	11.9 g/dl	Cl	97 mmol/l
Hct	35.1%	Ca	6.7 mg/dl
Plt	27.4×10^4/μl	BUN	8.6 mg/dl
		Cre	0.81 mg/dl
Coagulation		eGFR	60.2 ml/min
PT	60.0%	TP	4.6 g/dl
PT-INR	1.41	Alb	1.7 g/dl
APTT	73.0 s	T-bil	0.4 mg/dl
FDP	10.9 μg/ml	AST	47 IU/l
D-dimer	4.65 μg/ml	ALT	32 IU/l
		CRP	21.92 mg/dl
		PCT	0.25 ng/ml

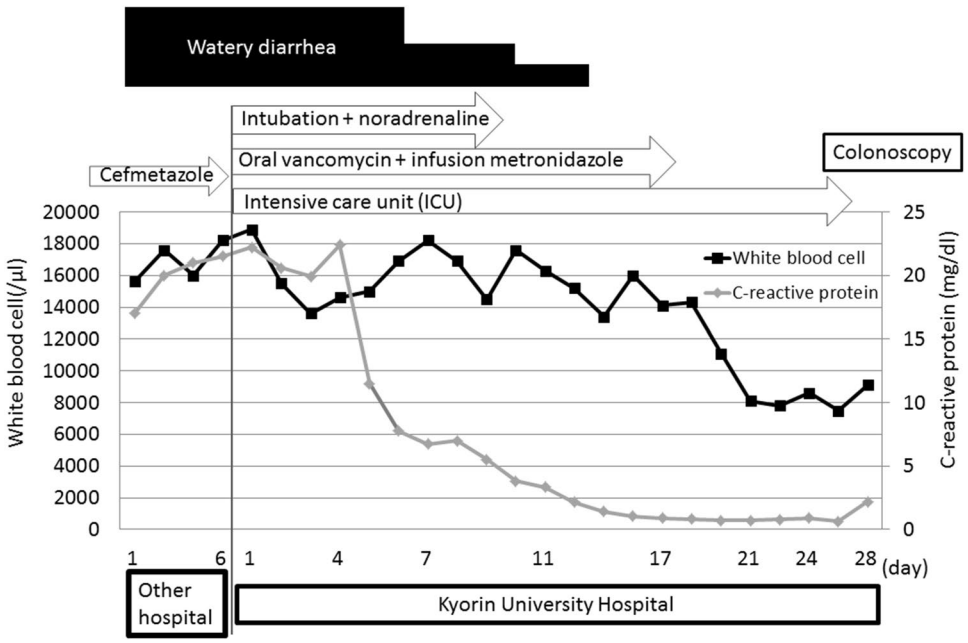

Fig. 1 Patient's clinical course

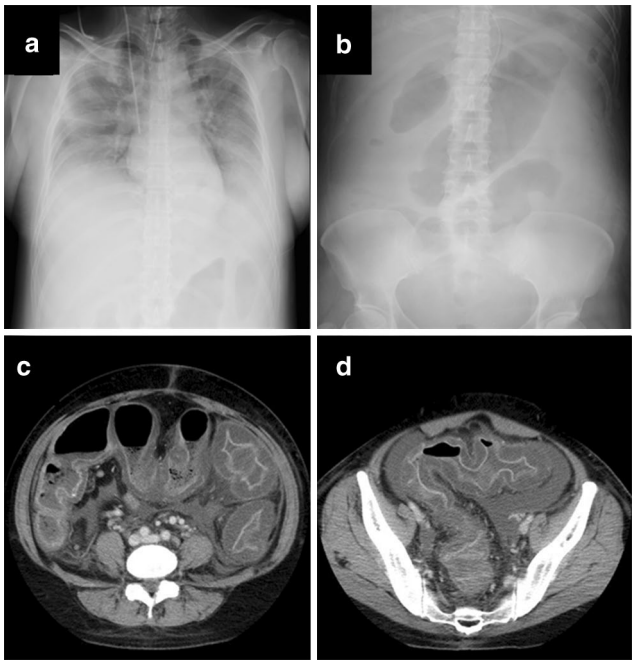

Fig. 2 X-ray and CT findings: **a** pleural effusion was observed. **b** The transverse colon expanded to a diameter of 8 cm. **c, d** Ascites and marked colonic mucosal edema were observed

Since the patient had circulatory insufficiency and respiratory failure, intubation was performed and a strong dose of noradrenaline was administered in the intensive care unit (ICU). For her initial CDI treatment, we began administering metronidazole infusion at 1500 mg/day and oral vancomycin at 2000 mg/day. Probiotics that produce *Clostridium butyricum* (Miya-BM®) were also administered. Clinical symptoms and blood levels of white blood cells, C-reactive protein, coagulability and nutritional status gradually improved. She was extubated on the 11th hospital day, and the antibiotic therapy was discontinued on the 17th hospital day. After her general condition improved on the 30th hospital day, colonoscopy of the whole colon was performed. The results showed bowel wall edema, erythema, friability, and multiple ulcers; however, no obvious pseudomembrane formation was observed (Fig. 3).

The *C. difficile* isolate that was recovered upon admission in our hospital was analyzed. PCRs detecting the toxin genes were carried out, and the isolate was identified as toxin A-positive, B-positive and binary toxin-positive. By PCR ribotyping and *slpA* sequence typing, the isolate was typed as PCR ribotype ts0592/*slpA* sequence type ts0592-01 (Fig. 4).

Discussion

C. difficile is an obligatory anaerobic, gram-positive rod organism that forms spores and persists in healthcare facilities [6]. Clinical symptoms of CDI vary from mild diarrhea

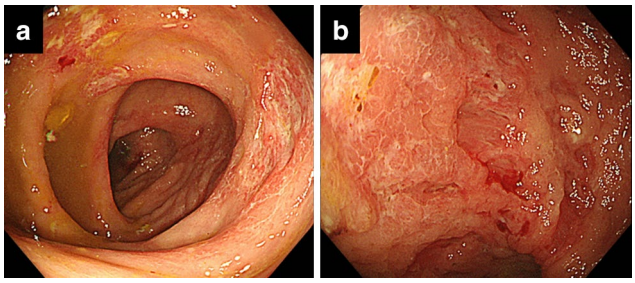

Fig. 3 Colonoscopic findings in sigmoid colon: **a, b** Colonoscopy revealed bowel wall edema, erythema, friability, and multiple ulcers in whole colon. However, obvious pseudomembrane formation was not observed

to severe cases with pseudomembrane formation, toxic megacolon, cardiopulmonary failure, and death. CDI occur due to disruption of normal intestinal flora. Probiotics in CDI have been suggested to recover intestinal flora [7]. Our case of community-acquired CDI involved a 46-year-old non-elderly woman with no history of antibiotic use. A study of all confirmed CDI cases in a Minnesota county between 1991 and 2005 demonstrated that the incidence of both community-acquired and hospital-acquired infections increased dramatically during the study period. Approximately 41% of these cases were community-acquired. Patients with community-acquired infections were younger (median age 50 years versus 72 years), healthier, and more likely to be female (76% versus 60%) than those with hospital-acquired infections [8]. CDI was traditionally recognized as a nosocomial infection accompanying the use of antibiotics; however,

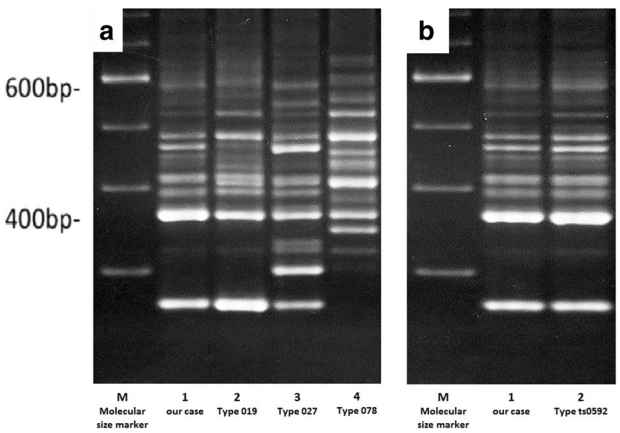

Fig. 4 The result of PCR ribotyping which is strains genetic identification by electrophoresis. **a** Comparison between our case and highly virulent strains of type 019, 027, 078 prevailed in Europe and North America. Our case did not match any strain. **b** Comparison between our case and type ts0592 matched by *slpA* sequence typing. The band pattern of our case was consistent with type ts0592. The isolate of our case was typed as PCR ribotype ts0592

Dials et al. found that among community-acquired infection cases, approximately 50% of the patients received no antibiotic therapy within the last 90 days [9].

The isolate which caused fulminant colitis in the healthy non-elderly woman with no major risk factors of CDI was binary toxin-positive and identified as PCR ribotype ts0592/*slpA* sequence type ts0592-01.

Several genetic analyses aimed at improving epidemiologic analyses and characterization of *C. difficile* have been developed. PCR ribotyping, which is a typing system based on the difference in amplification products of the 16S–23S rRNA gene intergenic spacer region, has been used as the most common method in Europe [10]. Typing by sequencing *slpA* encoding the surface layer protein A (SlpA) which is part of the bacterial outer membrane is also one of the genetic schemes for typing *C. difficile* [11].

As one of binary toxin-positive strains, PCR ribotype 027 had prevailed in Europe and North America in the 2000s [12]. The emergence of CDI due to PCR ribotype 078, which had been the predominant type in pigs and calves [13], was also reported to be found in humans [4]. The two binary toxin-positive strains have been attracting attention in Europe and North America, where they are epidemic or endemic, because they may be associated with the severity of the disease outcome [2, 4].

The isolate obtained from our case was binary toxin-positive but neither PCR ribotype 027 nor 078. There have been a few reports of fulminant CDI cases caused by binary toxin-positive *C. difficile* in Japan [14, 15], although no outbreaks have been reported. Among more than 500 *C. difficile* isolates collected in Japanese facilities, there were only four isolates that belonged to *slpA* sequence major type ts0592 (subtypes ts0592-01 or ts0592-02). *C. difficile* identified as *slpA* sequence subtype ts0592-02 caused fulminant colitis leading to death in two patients at the same hospital [15]. Another *slpA* sequence subtype ts0592-02 *C. difficile* was found in a woman in her thirties who was diagnosed with community-acquired pseudomembranous colitis in 2011 (data not shown). The demographic information of the patient, whose remaining type (*slpA* sequence subtype ts0592-01) was isolated, was not available. Among these five *slpA* sequence type ts0592 isolates including that from the present case, three different PCR ribotypes were identified. It should be noted that four of five cases with *slpA* sequence type ts0592 *C. difficile* had severe diseases. In addition, two of these patients were young and CDI was community-acquired. *SlpA* sequence type ts0592 may play a significant role in disease severity and may have some virulence factors other than binary toxin. However, isolation of the type is rare, and case accumulation is necessary.

There are currently a few investigations on the molecular epidemiology of CDI [16], especially of community-acquired infections, in Japan. Further studies are required to clarify the potential significance of binary toxin-producing *C. difficile* strains including *slpA* sequence type ts0592 strains in enteritis patients without risk of CDI in Japan.

Acknowledgements This research was partially supported by AMED under Grant number JP 18fk0108049j2302.

Compliance with ethical standards

Conflict of interest All authors (Noriaki Oguri, Akihito Sakuraba, Hirom Morikubo, Oki kikuchi, Taro Sato, Soutaro, Tokunaga, Shintaro Minowa, Osamu Ikezaki, Tatsuya Mitsui, Miki Miura, Daisuke Saito, Mari Hayashida, Hideaki Mori, Takako Osaki, Shigeru Kamiya, Mitsutoshi Senoh Haru Kato and Tadakazu Hisamatsu) declare that they have no conflict of interest.

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. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353:2442–9.
2. Miller M, Gravel D, Mulvey M, et al. Health care-associated *Clostridium difficile* infection in Canada: patient age and infecting strain type are highly predictive of severe outcome and mortality. Clin Infect Dis. 2010;50:194–201.
3. Gerding DN, Johnson S, Rupnik M, et al. *Clostridium difficile* binary toxin CDT: mechanism, epidemiology, and potential clinical importance. Gut Microbes. 2014;5:15–27.
4. Goorhuis A, Bakker D, Corver J, et al. Emergence of *Clostridium difficile* infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. Clin Infect Dis. 2008;47:1162–70.
5. Kato H, Ito Y, van den Berg RJ, et al. First isolation of *Clostridium difficile* 027 in Japan. Euro Surveill. 2007;12:E070111.3.
6. Mayfield JL, Leet T, Miller J, et al. Environmental control to reduce transmission of *Clostridium difficile*. Clin Infect Dis. 2000;31:995–1000.
7. Japanese Society of Chemotherapy Committee on Guidelines for Treatment of Anaerobic Infectious. Japanese Association for Anaerobic Infection Research: Chap. 2-12-7. Anaerobic infections (individual fields): antibiotic-associated diarrhea and enterocolitis. J Infect Chemother. 2011;17:137–9.
8. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired *Clostridium difficile* infection: a population-based study. Am J Gastroenterol. 2012;107:89–95.
9. Dial S, Kezouh A, Dascal A, et al. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. CMAJ. 2008;179:767–72.
10. Stubbs SL, Brazier JS, O'Neill HL, et al. PCR targeted to the 16S–23S rRNA gene intergenic spacer region of *Clostridium difficile* and construction of a library consisting of 116 different PCR ribotypes. J Clin Microbiol. 1999;37:461–3.
11. Kato H, Kato H, Ito Y, et al. Typing of *Clostridium difficile* isolates endemic in Japan by sequencing of *slpA* and its application to direct typing. J Med Microbiol. 2010;59:556–62.

12. He M, Miyajima F, Roberts P, et al. Emergence and global spread of epidemic healthcare-associated *Clostridium difficile*. Nat Genet. 2013;45:109–13.
13. Keel K, Brazier JS, Post KW, et al. Prevalence of PCR ribotypes among *Clostridium difficile* isolates from pigs, calves, and other species. J Clin Microbiol. 2007;45:1963–4.
14. Nishimura S, Kou T, Kato H, et al. Fulminant pseudomembranous colitis caused by *Clostridium difficile* PCR ribotype 027 in a healthy young woman in Japan. J Infect Chemother. 2014;20:729–31.
15. Tagashira Y, Kato H, Senoh M, et al. Two cases of fulminant colitis due to binary toxin-positive *Clostridium difficile* that are not PCR ribotype 027 or type 078. J Med Microbiol. 2013;62:1486–9.
16. Senoh M, Kato H, Fukuda T, et al. Predominance of PCR-ribotypes, 018 (smz) and 369 (trf) of *Clostridium difficile* in Japan: a potential relationship with other global circulating strains? J Med Microbiol. 2015;64:1226–36.