

[CASE REPORT]

***Vibrio cholerae* Infection in Japan Not Associated with Overseas Travel**

Masao Tatebe¹, Asako Doi², Seiko Nasu³, Natsuki Hama⁴, Ryohei Nomoto⁴, Eiji Arakawa⁵,
Hidemasa Izumiya⁵ and Hiroaki Nishioka²

Abstract:

A 74-year-old Japanese man who was taking antacids presented with profuse diarrhea. Stool culture revealed *Vibrio cholerae* O1 strain, serogroup Ogawa, biotype El tor. He recalled he had consumed some sashimi but denied any history of travelling abroad, and another cholera case with almost the same strain was reported at the same time in a remote prefecture in the Kanto area. This is a rare case of travel-unrelated cholera in Japan, and it illustrates the importance of suspecting cholera in all patients presenting with large volumes of watery diarrhea in Japan, especially in those who are taking antacids, regardless of their international travel history.

Key words: cholera, *Vibrio cholera* O1, antacid, travel unrelated

(Intern Med 58: 2581-2583, 2019)

(DOI: 10.2169/internalmedicine.2639-19)

Introduction

Cholera, an intestinal infection caused by *Vibrio cholerae*, is characterized by acute watery diarrhea without abdominal pain. In severe cases, a large volume of diarrhea may lead to rapidly progressive dehydration and shock. In recent years, only a few cases of cholera have been reported annually in Japan, where the environment does not naturally harbor toxigenic strains of *V. cholerae*; accordingly, nearly all reported cases have been imported from abroad (1).

We herein report a rare case of cholera in a Japanese patient who had not travelled internationally, with another concurrent cholera case found caused by a seemingly identical strain in a remote area of Japan.

Case Report

A 74-year-old Japanese man sought care after experiencing a large volume of watery diarrhea and nausea without abdominal pain, with his symptoms worsening over a 2-day period. On the day of admission, he produced 10-20 bowel

movements per day and became anuric. He reported no travel history and had not had any contact with any people with similar symptoms. Three days prior to the onset of symptoms, he had eaten some sashimi that he had purchased at a supermarket the same day. His medical history included chronic kidney disease with a creatinine level of 1.26 mg/mL, diabetes mellitus with HbA1c 6.8%, nontuberculous mycobacterial pulmonary disease, hyperuricemia, and hypertension. He had been taking esomeprazole 20 mg/day, nifedipine 40 mg/day, olmesartan 40 mg/day, pitavastatin 2 mg/day and alogliptin 12.5 mg/day.

On a physical examination, his body temperature was 36.4°C, respiratory rate 18 breaths/min, pulse rate 77 beats/min, and blood pressure 108/52 mmHg. He was alert and conscious. He had increased bowel peristalsis and abdominal distention with diffuse tenderness. The skin turgor was slightly decreased. Laboratory tests showed a white blood cell count of 10,200/ μ L, hemoglobin level of 13.6 g/dL, platelet count of 36.2×10^4 / μ L, blood urea nitrogen of 30.5 mg/dL, creatinine of 2.83 mg/dL, Na 138 mEq/dL, K 3.8 mEq/dL, Cl 106 mEq/dL and C-reactive protein level of 1.81 mg/dL. Abdominal computed tomography without con-

¹Department of Emergency, Kobe City Medical Center General Hospital, Japan, ²Department of Infectious Diseases, Kobe City Medical Center General Hospital, Japan, ³Department of Laboratory Medicine, Kobe City Medical Center General Hospital, Japan, ⁴Kobe Institute of Health, Kobe, Japan and ⁵National Institute of Infectious Diseases, Japan

Received: January 10, 2019; Accepted: March 17, 2019; Advance Publication by J-STAGE: June 7, 2019

Correspondence to Dr. Asako Doi, asakodoi@gmail.com

trast revealed extensive bowel edema. His stool culture grew *V. cholerae* O1, Ogawa serogroup, biotype El tor in thiosulfate citrate bile sucrose (TCBS) agar. The cerebrotendinous xanthomatosis (CTX) toxin gene was detected from the organism, and the toxin concentration was 8 ng/mL (VET-RPLA, Denka-Seiken).

We administered an isotonic crystalloid solution at a rate of 100 mL/minute. Antibiotics were not provided since his condition began to improve upon the identification of the organism. He began to urinate 2 days after admission, and the frequency of his bowel movements decreased from day 4. Fluid replacement was decreased, and he began to eat from day 6. His creatinine level increased to 7.61 mg/dL at 4 days after admission, but it gradually decreased again and had returned to the basal level by 1 month after discharge. He was discharged home on day 12.

A detailed investigation of the potential sources of *V. cholerae*, including the water supply, sewerage and living environment, failed to identify the route of infection. No additional patients with cholera among the patient's family or friends, food handlers or customers of the supermarkets were identified. However, another case of *V. cholerae* infection unrelated to international travel was reported in the eastern Kanto area, quite far from Kobe, which is located in the western part of Honshu island, at a very similar timing; furthermore, these strains turned out to be identical according to a multilocus variable-number repeat analysis (MLVA) (1) conducted by the National Institute of Infectious Diseases, although no further investigation regarding the potential outbreak was performed.

Discussion

Cholera is endemic in Africa, Asia, the Middle East, South and Central America and the Caribbean, where approximately 2.8 million cases and approximately 91,000 related deaths are reported annually (2). Cholera-related mortality can reach up to 50% without rehydration therapy, but effective fluid replacement can decrease mortality to less than 0.2% (3-5). Risk factors for cholera include insufficient access to clean water, reduced immunity and taking antacids, as antacids can allow smaller numbers of *V. cholerae* to cause disease by impairing the gastric acid barrier (4).

Outbreaks of cholera occurred in Japan both in 1882 and 1895, with 802 and 604 respective cases reported in the northern Kanto area (6). However, the incidence of cholera dramatically decreased in Japan in the 20th century. In 1997, 36 cases with no history of international travel were reported to national surveillance (7), and thereafter, only 95 domestic cases were reported from 1999 to 2008, while 332 imported cases occurred during the same period (8). A survey revealed that *V. cholerae* was not detected in natural water in Japan (9). These findings suggest that all cases of cholera in Japan are likely due to either imported strains or patients or are secondary cases infected by these sources.

Unfortunately, we were unable to identify the source of *V.*

cholerae in the current case, and while seemingly the same strain was detected in the Kanto area, far away from Kobe, at the same time, no epidemiological link was identified. The reason why only a few cases of cholera were detected during the current outbreak remains unclear, but given the small amount of cholera toxin found in our case, namely only 8 ng/mL with a relatively low inoculum of *V. cholerae*, these findings suggest that there might have been some undetected mild cases or even asymptomatic cases in Japan that were contracted by consuming either imported contaminated seafood or water discarded from the ballasts of international tankers, as reported previously (10, 11). The possibility of secondary transmission from a returned traveler cannot be excluded, but this is less likely given that no such contact was noted after our detailed history taking. The purpose of this case report is not to investigate epidemiological links but rather to demonstrate that domestic cases of cholera can still manifest, regardless of the origin of infection.

Regarding the risk factors for cholera in the current patient, antacid use may have been the cause of his symptomatic disease, as in other cases of enteric infection. Esomeprazole use had never been linked to clinical cholera cases, as far as we were able to determine through our literature search, but the potential overuse of antacids, such as proton pump inhibitors, might increase the risk of enteric infections, such as cholera (12). Further studies should be conducted to determine the role of proton pump inhibitors on the pathogenesis of cholera.

In addition to the risk of importing *V. cholerae* from abroad, recent global warming may also expand the endemic area of cholera, as *V. cholerae* grows optimally in warm waters (i.e. 30°C), such as those found in tropical climates (13, 14). This suggests that attention should be directed toward the potential for future *V. cholerae* endemicity in areas where few cases are currently reported, like Japan.

In conclusion, we have described our experience with an apparently domestic case of cholera in Japan. The source appears to be imported food or unidentified transmission from a returned traveler, although the source could not be confirmed, and the infection developed while the patient was taking esomeprazole. This case emphasizes that cholera should be suspected in patients who present with large volumes of watery diarrhea, even in Japan, regardless of the history of international travel and particularly when the patient has been taking antacids. In the future, global warming might increase the number of similar cases in developed countries, such as Japan, where *V. cholerae* is not currently endemic.

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

Acknowledgement

We thank Dr. Akihiro Ijichi, Chief of the Public Health Center of Kobe, for providing the results of an epidemiological investigation involving this case.

References

- Morita M, Ohnishi M, Arakawa E, et al. Emergence and genetic diversity of El Tor *Vibrio cholerae* O1 that possess classical biotype ctxB among travel-associated cases of cholera in Japan. *J Med Microbiol* **59**: 708-712, 2010.
- Ali M, Lopez AL, You YA, et al. The global burden of cholera. *Bull World Health Organ* **90**: 209-218, 2012.
- Harris JB, LaRocque RC, Qadri F, Ryan ET, Calderwood SB. Cholera. *The Lancet* **379**: 2466-2476, 2012.
- Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. *The Lancet* **390**: 1539-1549, 2017.
- Moore S, Thomson N, Mutreja A, Piarroux R. Widespread epidemic cholera caused by a restricted subset of *Vibrio cholerae* clones. *Clin Microbiol Infect* **20**: 373-379, 2014.
- Kuo C-L, Fukui H. Geographical structures and the cholera epidemic in modern Japan: Fukushima prefecture in 1882 and 1895. *Int J Health Geogr* **6**: 25, 2007.
- National Institute of Infectious Diseases. National cholera information from 1997 to 2011 [Internet]. [cited 2018 Dec 9]. Available from: <https://www.niid.go.jp/niid/ja/id/995-disease-based/ka/cholerae/idsc/iasr-in/1120-iasr-d-1997-2011.html> (in Japanese).
- Taniguchi K, Yoshida M, Sunagawa T, Tada Y, Okabe N. Imported infectious diseases and surveillance in Japan. *Travel Med Infect Dis* **6**: 349-354, 2008.
- Minami A, Hashimoto S, Abe H, et al. Cholera enterotoxin production in *Vibrio cholerae* O1 strains isolated from the environment and from humans in Japan. *Appl Environ Microbiol* **57**: 2152-2157, 1991.
- Huehn S, Eichhorn C, Urmsbach S, et al. Pathogenic vibrios in environmental, seafood and clinical sources in Germany. *Int J Med Microbiol* **304**: 843-850, 2014.
- Rivera ING, Souza KMC, Souza CP, Lopes RM. Free-living and plankton-associated vibrios: assessment in ballast water, harbor areas, and coastal ecosystems in Brazil. *Front Microbiol* **3**: 443, 2013.
- Armand L. Potent acid reduction and risk of enteric infection. *Lancet* **335**: 222, 1990.
- Pruzzo C, Vezzulli L, Colwell RR. Global impact of *Vibrio cholerae* interactions with chitin. *Environ Microbiol* **10**: 1400-1410, 2008.
- Chowdhury FR, Nur Z, Hassan N, von Seidlein L, Dunachie S. Pandemics, pathogenicity and changing molecular epidemiology of cholera in the era of global warming. *Ann Clin Microbiol Antimicrob* **16**: 10, 2017.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).