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Case Report

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A Fatal Case of Bacteremia Caused by *Vibrio cholerae* Non-O1/O139

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ABSTRACT

Vibrio cholerae is a pathogen known to cause the waterborne epidemic disease cholera. Overall, *V. cholerae* O1 or O139 strains produce the cholera toxin that cause gastroenteritis, resulting in watery diarrhea. Most of the enterocolitis caused by *V. cholerae* can be easily treated with fluid therapy and conservative care. However, *V. cholerae* non-O1/O139 strains can cause extraintestinal infections, such as wound infection or sepsis, in immunocompromised patients. The clinical course of these infections is very similar to that of *V. vulnificus* infection. We report about a 52-year-old man without previous underlying disease who was diagnosed with *V. cholerae* non-O1/O139 infection and died within 72 hours after admission to the intensive care unit.

Keywords: *Vibrio cholerae*; Non-O1/O139; Septic shock

INTRODUCTION

Vibrio cholerae is an aquatic, environmental Gram-negative bacterium, which is able to cause life-threatening disease in humans [1]. More than 200 serogroups of *V. cholerae* have been identified, though only serogroups O1 and O139 are typically toxigenic and cause cholera outbreaks. Cholera is one of the deadliest enteric diseases worldwide, and is acquired from contaminated water and food in many parts of Asia, Africa, and Latin America [2]. In contrast, *V. cholerae* non-O1/O139 strains do not produce cholera toxins, and their significance has been usually overlooked thus far. However, recent reports have shown that non-O1/O139 strains can cause fatal extraintestinal infections [3, 4]; thus, the clinical importance of these strains is increasing. The mortality rate associated with *V. cholerae* non-O1/O139 bacteremia has been shown to depend on the studied cohort, and varies from 24% to 61.5% [5]. In Korea, *V. cholerae* non-O1/O139 infection is rarely reported. To the best of our knowledge, only four cases have been reported in Korea, all involving patients who were immunocompromised, due to liver cirrhosis, cancer or uncontrolled diabetes [3, 6-8]. Here, we report a case of a healthy 52-year-old man who died due to *V. cholerae* non-O1/O139 infection. He died within 72 hours after admission, despite having been aggressively treated in the intensive care unit (ICU).

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No conflicts of interest.

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Conceptualization: SWK, SYH, HIK. Methodology: SJK, HKP, JML. Writing - original draft: SYH, YJK, HJJ. Writing - review & editing: SWK, HHC.

CASE REPORT

A 52-year-old man visited the Daegu Fatima Hospital, in Daegu, Korea, in September 2017. He had been previously hospitalized due to watery diarrhea, chills and fever after eating slices of raw fish four days before hospitalization. The patient had no relevant medical history; however, he reported the habit of drinking 1 - 2 bottles of soju, a Korean alcoholic beverage (each bottle of soju contains 50 g of pure alcohol) almost every day in the last four years. The suspected diagnosis was *V. vulnificus* infection and the patient received fluid therapy and intravenous antibiotic therapy (cefotaxime 2 g every 8 hours); however, the fever persisted and blisters were detected on the right leg on the second day. He was then referred to our hospital and admitted to the ICU.

On admission, his vital signs were as follows: body temperature of 38°C; blood pressure of 73/40 mmHg; pulse rate of 100 beats per minute; and respiratory rate of 40 breaths /min. Upon examination, he was alert and cooperative but looked acutely ill, with mild pallor and icteric sclera. His lower extremities had no edema, but blisters with ecchymosis were observed on his right calf (**Fig. 1A**).

A complete blood count showed hematocrit level of 26.6%, white blood cell count of 3,230 cells/mm^3 (75.8% were polymorphonuclear cells), and platelet count of 41,000 cells/mm^3. Venous blood gas analysis revealed a pH of 7.306, and carbon dioxide tension of 25.7 mmHg, partial pressure of oxygen of 29.7 mmHg, bicarbonate level of 13.0 mmol/L, base excess of 11.4 mmol/L, oxygen saturation level of 49.7%, and lactic acid level of 15.8 mmol/L (normal range: 0.7 - 2.1 mmol/L). Serum C-reactive protein concentration was 6.52 mg/dL (normal range: 0.0 - 0.5 mg/dL) and serum procalcitonin concentration was 57.030 ng/mL (normal range, 0.0 - 0.100 ng/mL). Measurement of serum concentrations of liver function markers showed the following results: total bilirubin, 2.85 mg/dL; direct bilirubin, 2.3 mg/dL; alkaline phosphatase, 65 U/dL; aspartate transaminase, 181 U/dL; alanine transaminase, 35 U/dL; albumin, 2.5 g/dL; and total protein, 5.6 g/dL. Coagulation tests showed prothrombin time of 25.1 s (normal range: 10 - 14 s); partial thromboplastin time of 85.5 s (normal range: 20 - 40 s), and international normalize ratio of 2.32. Serum concentrations of urea nitrogen and creatinine

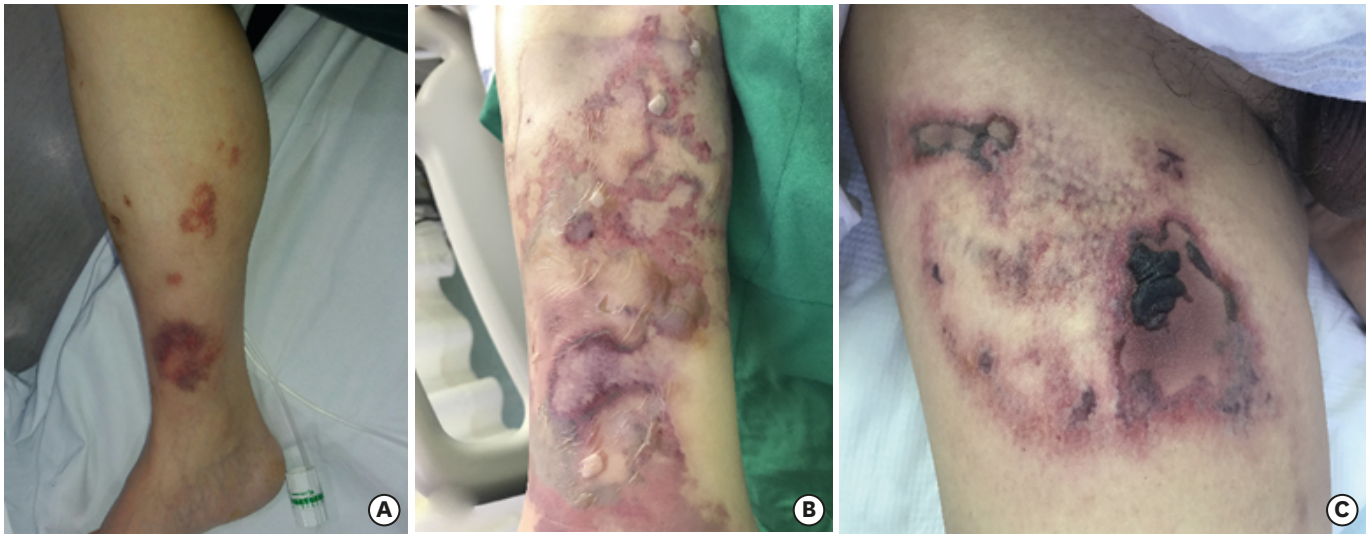

Figure 1. Skin lesion on patient's right lower leg and thigh (A) Right calf, first day. (B) Right calf, second day. (C) Right thigh, second day.

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were 34.4 mg/dL and 3.66 mg/dL, respectively. We checked hemoglobin A1c to evaluate whether the patient had diabetes or not, and the result (5.2%) within the normal range.

Plain chest radiograph was compared to radiograph obtained from the hospital where the patient had been previously admitted to, on the day he was referred to our hospital (**Fig. 2A**). Newly formed pulmonary shadows were observed in both lobes in six hours (**Fig. 2B**). No abnormal results were found on abdominal and chest computed tomography (CT) scans obtained on the day before admission to our hospital. The interpretation of the image findings was limited, since no contrast medium was used when the CT scans were performed, but there were no suspicious findings of liver cirrhosis or hepatic cancer (**Fig. 3**).

The patient underwent intravenous corticosteroid therapy (hydrocortisone 50 mg every six hours) and continuous infusion of inotropic agents (dopamine [15 μg/min/kg] and norepinephrine [0.5 μg/min/kg]) immediately after having a septic shock, and empirical

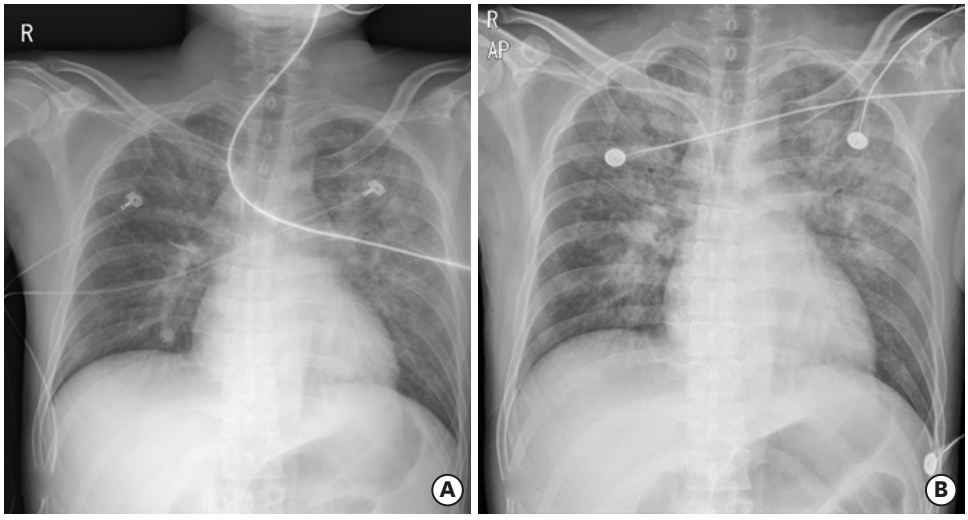

Figure 2. Simple chest radiography (A) in the morning of the day when the patient was referred to our hospital. (B) Bilateral diffuse opacities emerged in six hours, suggesting newly developed acute respiratory distress syndrome.

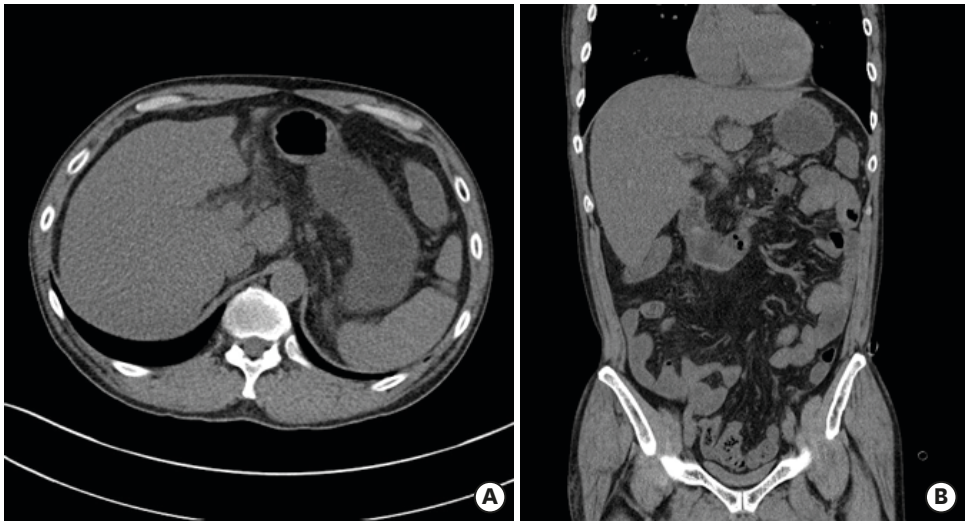

Figure 3. Axial (A) and sagittal (B) abdominal computed tomography imaging shows no nodular liver contour.

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intravenous antibiotic therapy (cefepime 1 g every 24 hours and oral doxycycline 100 mg twice a day) were administered after performing three pairs of blood cultures. Twelve hours after admission, metabolic acidosis had not improved. Arterial blood gas analysis revealed a pH of 7.388, carbon dioxide tension of 23.5 mmHg, bicarbonate level of 14.3 mmol/L, and oxygen saturation level of 83.8% using an oxygen mask 10 L/min, so ventilator therapy started after tracheal intubation. On the second day, the blood pressure was restored and maintained in the normal range without inotropes. However, hemorrhagic blisters developed on the right calf (**Fig. 1B**) and then spread to the right thigh (**Fig. 1C**). After the urine output decreased to <30 mL/hr and central venous blood pressure increased to ≥15 mmHg, continuous renal replacement therapy was initiated. On the third day, the metabolic acidosis worsened and the patient developed multiple organ failure. Arterial blood gas analysis revealed a pH of 7.100, carbon dioxide tension of 40.9 mmHg, partial pressure of oxygen of 71.6 mmHg, bicarbonate level of 12.4 mmol/L, base excess of 17.2 mmol/L, oxygen saturation level of 88.1%, and lactic acid level of 19.5 mmol/L. Serum aspartate aminotransferase and alanine aminotransferase levels rapidly increased to 5,852 U/dL and 455 U/dL, respectively, and total bilirubin and direct bilirubin levels increased to 7.22 mg/dL and 5.65 mg/dL, respectively. Creatine phosphokinase and lactate dehydrogenase levels were 75,885 U/L and 8,433 U/L, respectively. Despite administration of high doses of inotropic agents (dopamine [22.5 μg/min/kg], norepinephrine [1.4 μg/min/kg] and epinephrine [0.10 μg/min/kg]), the patient died of septic shock 72 hours after admission.

Blood cultures performed at the Daegu Fatima Hospital showed Gram-negative rods. Subculture in thiosulfate-citrate-bile salts-sucrose agar revealed oxidase-positive yellow colonies, similar to *V. cholerae*. Further identification testing was performed using conventional biochemical tests and the VITEK II Compact (BioMérieux, France). The organism was identified as *V. cholerae* with a 98% probability, but the susceptibility report did not come out. Serological tests identified the bacterium as a *V. cholerae* non-O1/O139 after no agglutination with the *V. cholerae* O1 and O139 polyvalent antisera. The presence of virulence genes was assessed by a polymerase chain reaction test, which was negative for the cholera toxin gene (*ctx*A), *V. cholerae* O139 O antigen-specific gene (*rfb*A), and *V. cholerae* O1 O antigen-specific gene (*rfb*B). Finally, the strain was confirmed to be a *V. cholerae* non-O1/O139 by the Daegu Public Health and Environment Research Institute.

This study was approved by the Institutional Review Board of the Kyungpook National University Medical Center of Korea with a waiver of informed consent (Subject number: 2020-08-002).

DISCUSSION

In this report, we describe a case of *V. cholerae* non-O1/O139 infection in a 52-year-old man. Despite a history of four years of alcohol consumption, he had never been diagnosed with liver cirrhosis or diabetes, and abdominal CT scan did not show suspicious lesion indicative of chronic liver disease on admission. To the best of our knowledge, this is the first case of death of a patient without underlying disease due to sepsis after *V. cholerae* non-O1/O139 infection reported in Korea.

Vibrio species are Gram-negative, rod-shaped (comma shape) bacteria, and several species of them can act as human pathogens. The three major pathogenic (or clinically important)

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Vibrio spp. are *V. cholerae*, *V. parahaemolyticus*, and *V. vulnificus*. Vibrio infections can be caused by the consumption of contaminated or undercooked seafood, or by skin exposure to seawater [9, 10]. However, these three *Vibrio* spp. differ in symptomatology and mortality rates. In the case of *V. vulnificus* infection (the most fatal *Vibrio* infection), the main symptoms are severe sepsis and necrotizing fasciitis [11, 12]. Even with aggressive treatment, including surgical drainage, the mortality rate is approximately 50% worldwide, and most patients die within 48 hours after the onset of infection [10]. The main clinical manifestation of *V. cholerae* and *V. parahaemolyticus* infections is gastroenteritis, presenting with watery diarrhea, abdominal pain, nausea and vomiting. If a moderate to large water volume is depleted, antibiotic treatment is needed, but, in most cases, patients are treated with fluid therapy and conservative care [11, 12]. However, among the *V. cholerae* species, *V. cholerae* non-O1/O139 strains, which do not secrete the cholera toxin, can cause symptoms similar to as *V. vulnificus*, especially in patients with liver cirrhosis or immunodeficiency, leading to poor prognosis. [3, 4, 6, 7].

V. cholerae is divided into more than 200 serogroups, according to the O antigen (external part of the cell wall lipopolysaccharide), and *V. cholerae* O1 and O139 are the only serogroups that can produce the cholera toxin and cause epidemic and pandemic cholera [2, 5]. As mentioned earlier, while *V. cholera*e O1 and O139 mostly cause gastrointestinal infection, *V. cholerae* non-O1/ O139 strains can cause extraintestinal diseases, such as wound infection, ear infection or bacteremia, especially in patients with chronic liver disease and immunodeficiency [13, 14]. The virulence factors that allow *V. cholera*e non-O1/ O139 strains to cause bacteremia remains unknown, but hemolysin, enterotoxin, cytotoxin or cholera-like toxin possibly play a role [5, 15]. The pathogenicity is similar to that of *V. vulnificus*, which prevents serum bactericidal activity and phagocytosis by encapsulating the toxin [16]. *V. cholera*e non-O1/O139 strains are rare, but may lead to fatal bacteremia, and the number of studies reporting infections with these strains has been increasing recently, as well as the clinical importance of these strains [17, 18]. The cause of increased frequency of *Vibrio* infection is not known precisely, however, the main cause is the warming of coastal waters, which will contribute to the growth and persistence of *V. cholerae* [15, 16].

In the case of *V. cholerae* non-O1/O139 infection, symptoms of enterocolitis such as infection of *V. cholerae* O1 or O139 can be easily treated with fluid therapy and electrolytic correction alone. However, antimicrobial therapy is strongly recommended for extraintestinal infections, such as wound infection and bacteremia [19]. Although third-generation cephalosporins with tetracycline or fluoroquinolones are widely used [20], no definite treatment guideline on *V. cholerae* non-O1/O139 infection is available to date, as infections with this strain are rare and antibiotic susceptibility varies from region to region. The duration of treatment has not been determined as well, and ranges from 3 to 75 days, with a median of 14 days, depending on the patient's background, severity and clinical response [20].

In conclusion, *V. cholerae* non-O1/O139 infection could be life-threatening in patients with liver cirrhosis or immunodeficiency; however, with the recently increased incidence, infections have also been reported in healthy immunocompetent patients [1], like in the present case report. Therefore, if a wound infection or extraintestinal infection occurs in a patient with suspected *V. cholerae* infection, antibiotic therapy and special care should be initiated as soon as possible, even in patients without underlying disease, and *V. cholerae* non-O1/O139 infection should be considered. In addition, further research and treatment guidelines on *V. cholerae* non-O1/O139 infection are warranted.

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