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Review

Non-O1, non-O139 *Vibrio cholerae* septicemia at a tertiary care center in Beirut, Lebanon; a case report and review

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ABSTRACT

More clinical infections with non-O1, non-O139 *Vibrio cholerae* have been recently reported. These pathogens usually do not cause the epidemic and pandemic cases of cholera seen with choleragenic vibrios. However, they can still cause intestinal as well as extra-intestinal disease and can be associated with significant mortality. Herein, we present the first case of non-O1, non-O139 *Vibrio cholerae* septicemia reported in Lebanon since the beginning of the Lebanese waste crisis.

Contents

Introduction

Vibrio species are known halophilic facultative anaerobes that are ubiquitously found in marine environments [1]. Their survival is governed by the water's temperature and salinity; hence, their incidence in water and aquatic animals increases during summer [2]. Based on the surface O antigen, *Vibrio cholerae* are divided into 200 serogroups [3]. The non-O1, non-O139 *Vibrio cholerae* (NOVC) strains do not produce the cholera toxin and therefore do not cause cholera [4]. The clinical significance of these microorganisms has been neglected for quite a long time. However, in the last decades, more human infections have been linked to those species [5,6]. Furthermore, the true incidence of NOVC infections is thought to be underestimated due to under-diagnosis and lack of proper growth media in many laboratories. It is currently estimated that between 1 and 3.4% of acute diarrhea in both developing and developed countries is due to NOVC [1].

The most frequently reported NOVC infections are gastroenteritis, otitis, and soft tissue infections [1]. On the other hand, NOVC sepsis remains rare and poorly described. For example, in a previous retrospective study, primary and secondary bacteremias were seen in only 13 and 31% of NOVC infections [7]. Therefore, our understanding of its clinical and therapeutic aspects remains vague [1,4].

Invasive NOVC infections are mainly seen in immunocompromised hosts. The main risk factors for NOVC bacteremia are hepatic cirrhosis, other liver diseases, alcoholism, diabetes mellitus, and hematologic malignancies [1,7]. We report a case of NOVC cholangitis and septicemia in a pancreatic cancer patient in Beirut that

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caused a stir in the wake of the waste crisis in Lebanon that started in July 2015, when the main waste dump serving the Beirut and Mount Lebanon region shut down and piles of trash filled the public streets. To our knowledge, our case is the third reported case of NOVC bacteremia in Lebanon and the first after the 2015 Lebanese trash crisis.

Case report

A 74-year-old lady was admitted in September 2015 to the American University of Beirut Medical Center (AUBMC) in Lebanon for fever of 3 days duration associated with nausea, vomiting and right upper quadrant abdominal pain. Her medical history was relevant for diabetes mellitus and pancreatic adenocarcinoma with liver metastasis. The patient was on chemotherapy and her most recent session was one week earlier. She underwent hepaticojejunostomy 1 year prior to presentation. The patient is of Iraqi origin but a resident of Beirut. She had no history of travel within the preceding 2 years and her exposure to visitors from abroad was limited to a single guest from Iraq 2 months earlier.

On presentation, the patient had a temperature of 38.8 °C but was hemodynamically stable. Physical exam showed icteric sclera and right upper quadrant tenderness. Her white blood cell count was 6800/mm^3, with 85% neutrophils. Her SGOT, SGPT, alkaline phosphatase, gamma-glutamyl transferase, and direct bilirubin levels were significantly higher than her baseline. She also had high serum lactic acid, C-reactive protein, and procalcitonin levels. A CT of the abdomen with contrast showed signs of acute cholangitis. She was empirically started on imipenem. Routine blood cultures grew Gram-negative rods after 9 h of incubation. Using 2 commercial systems (Vitek and API 20 NE), the isolate was identified as *Vibrio cholera* susceptible to ciprofloxacin and all the other tested agents. The isolate was referred to the ministry of health and it was identified as NOVC.

Antibiotics were switched to ciprofloxacin 400 mg IV twice daily. Her symptoms improved after 4 days and she was discharged on oral ciprofloxacin 500 mg twice daily to complete a 14-day course of therapy.

Discussion

NOVC infections in humans are usually the result of exposure to contaminated water or seafood [5]. Nonetheless, a good percentage of patients deny such exposure, indicating other possible sources of transmission [1]. NOVC are usually associated with three clinical syndromes: wound and ear infections, mild to severe acute gastroenteritis, and bacteremias, the latter being the least common [1,4]. Moreover, other types of infections have also been described but less frequently [8–10].

The spread of such pathogens into the blood depends on the bacterial strain type and the immune status of the patient. Sepsis in healthy individuals is rare. Most reports of bacteremia are in patients with comorbidities, especially conditions leading to immune dysfunction. On the other hand, the majority of cases in immunocompetent hosts fall under self-limiting gastroenteritis, and ear or wound infections [1].

The first described case of NOVC bacteremia was in the US in 1974 [11]. Subsequently, more reports were published. One retrospective study from Taiwan reported 83 patients with a variety of NOVC infection presentations [7]. Acute gastroenteritis, biliary tract infection, and primary bacteremia were seen in 54%, 15% and 13% of cases, respectively. The rate of secondary bacteremia was 31%. Acute gastroenteritis and biliary tract infections each accounted for 32% of secondary bacteremia. Liver cirrhosis was more prevalent among those with primary bacteremia than patients with other infections [7].

More recently, one review described 350 cases of NOVC septicemia [1]. The male-to-female sex ratio was 3.3:1 and the median age was 56 years. The majority of patients had a predisposing condition (96%). The most frequently documented risk factors were cirrhosis (54%) followed by malignancy (20%). Only 25% had a clear source of infection; 54% attributed to seafood consumption and 30% to contaminated water. The clinical presentation of bacteremic patients varied. They most often presented with hypo or hyperthermia, abdominal pain and diarrhea. Some had jaundice and ascites, both of which were linked to cirrhosis rather than the infection itself. Almost 5% had abscesses, including hepatic, prostatic, cerebral and peritoneal abscesses. The mortality rate was 33%. Hypotension, confusion and coma were significant determinants of a higher mortality [1].

Only 2 cases of NOVC bacteremias in Beirut residents were previously reported [12]. The first patient was a 54-year old cirrhotic male with spontaneous bacterial peritonitis. The second patient was a premature female infant born in the setting of preterm, premature rupture of the membranes who developed NOVC septicemia few hours post-delivery. In both patients, NOVC was isolated in blood cultures. Epidemiological investigation revealed a history of seafood consumption in the former patient, 1 week prior to presentation. No clear source was identified in the second case but the patient's mother lived in the coastal area of the southern suburbs of Beirut, where seawater backflow might have contaminated the wells supplying drinking water to the neighborhoods. Fortunately, both cases had a favorable outcome with proper antimicrobial therapy [12].

The mechanism of bloodstream invasion by NOVC species is not well known. The seeding of bacteria into blood is likely via spread from intestines into the portal vein or the intestinal lymphatic system [1]. It is suggested that haemolysin produced by certain strains plays a role. The hemolytic property of this molecule and its ability to cause cell vacuolation likely contribute to bacterial invasion [13]. Furthermore, the strong link between cirrhosis and NOVC bacteremia might be explained by the anatomical and physiological changes seen with cirrhosis: (1) increased intestinal permeability secondary to mucosal inflammation and edema; (2) escape of hepatic reticuloendothelial system secondary to portal hypertension; (3) complement deficiencies, impaired phagocytosis and inefficient chemotaxis [1].

NOVC gastroenteritis in immunocompetent patients are mostly self-limited and do not require antibiotics. On the other hand, antimicrobials are recommended in complicated infections and in immunocompromised hosts [1]. In the absence of clinical trials, guidelines on the treatment of NOVC bacteremia are lacking and significant diversity in management is noticed from published case reports. Some authors recommend dual-agent therapy in NOVC bacteremia. Combining a third-generation cephalosporin with a tetracycline or a fluoroquinolone seems to be effective, depending on susceptibility results. The duration of treatment in septicemia is also controversial and has ranged in various reports from 3 to 75 days (a median of 14 days) [1].

In comparison with the above cases, our patient is an elderly female with comorbidities predisposing her to NOVC bacteremia. She developed secondary bacteremia due to biliary infection. She received ciprofloxacin as monotherapy and showed improvement within 4 days of admission. Her disease outcome was favorable with 14 days of antibiotics. No apparent source of transmission was identified in our patient; however, we believe that a possible source would be the consumption of contaminated water in Beirut.

In 2015, the main dumpsite serving the Beirut and Mount Lebanon areas closed and, consequently, rubbish piled up in the streets. Protests broke out due to failure of municipalities to pro-

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