

Non-O1/non-O139 *Vibrio cholerae* bacteraemia and cholangitis: An unusual case in an oncological patient in Lecco Hospital, Italy

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Abstract

Vibrio species are curved, motile, aerobic and facultative anaerobic, Gram-negative bacilli that are widely distributed in aquatic environments, especially marine and estuarine waters. *Vibrios* of primary concern in human pathology are essentially represented by the species *Vibrio cholerae*. Classification of *Vibrio cholerae* is based on the O-antigen polysaccharide type, with over 200 serogroups described. Historically, only toxigenic serogroups O1 and O139 have been associated with widespread cholera epidemics. Other serogroups can cause small outbreaks that spread via contaminated raw seafood (primarily shellfish and molluscs) and seawater exposure, and they are collectively termed Non-O1/Non-O139 *Vibrio Cholerae* (NOVC). NOVC, occasionally detected also in the Mediterranean Sea, most often causes sporadic gastrointestinal manifestations requiring supportive therapy. However, rarely the *V. cholerae* non-O1/non-O139 serotype can result in extraintestinal manifestations such as severe wound infections, soft tissue infections and sepsis in immunocompromised patients that represent a therapeutic challenge. In particular, NOVC bacteraemia is a rare event but has the highest mortality rates among NOVC infections (almost 33%) and usually occurs in certain immunosuppressed populations, such as patients with haematologic and solid malignancies, and those with underlying liver disease.

Keywords: Patient; Infections; Liver disease.

Case Presentation

We report the case of a 46-years-old woman who was admitted to the emergency department of Hospital A. Manzoni in Lecco presenting fever with chills, nausea and abdominal pain. Her medical history was relevant for GERD and Von Hippel-Lindau syndrome characterized by cervical and cauda equina spinal hemangioblastomas and pancreatic neuroendocrine carcinoma G3 with hepatic and renal metastases. She underwent duodeno-cephalo-pancreatectomy in 2014 and left hepatectomy with atypical right hepatic

rsections in 2020. She was also treated with several lines of systemic therapies (sunitinib, capecitabine with temozolomide and Lutetium [¹⁷⁷Lu] oxodotreotide) and with somatostatin analogue until June 2023. In July 2023, she started Everolimus, poorly tolerated due to the development of neutropenia and mucositis. On admission, she had fever (39.9°C) and hypotension (BP 80/50). Laboratory findings demonstrated a WBC count of 2500/uL (N 86%), a PLT count of 54000/uL, CRP of 23.12 mg/dL, PCT of 2.18 ng/mL, mild hypertransaminasemia but normal blood bilirubin and glucose. Chest and abdominal CT scan was performed and revealed an acute cholangitis with thickening and increased enhancement of the common bile duct. Consequently, blood cultures were drawn and empiric antibiotic therapy with piperacillin/tazobactam was initiated. Standard stool cultures were negative. Blood cultures were incubated in an automatic blood culture detection system (BacT/Alert Virtuo, BioMérieux). Both anaerobic and aerobic blood culture bottles grew comma shaped Gram-negative bacilli at around 6 h. After subculture on an appropriate solid agar medium (Chocolate agar, bioMérieux) and rapid incubation at 35°C in CO₂, a preliminary identification with Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS) was performed and revealed *V. cholerae* with 99.9% probability. The same identification was confirmed with the automated VITEK 2 compact system using the ID-GN card (bioMérieux).

A subculture was performed adding a Thiosulfate-Citrate-Bile Salts-Sucrose agar (TCBS) plate to the agar plates routinely cultured. The following day beta-haemolytic mucoid colonies of curved, oxidase-positive, facultative anaerobic Gram-negative bacilli grew on 5% sheep blood agar plates and non lactose-fermenter colonies on Mac Conkey agar. Yellow colonies grew on thiosulfate-citrate-bile salts-sucrose agar, as well. Considering the microbiological findings, a more detailed medical history was then collected, and the patient reported the consumption of oysters from France bought at the supermarket five days before the onset of the symptoms. Also, multiple stool cultures specific for *V. cholerae* were performed, and they all tested negative. The strain was therefore sent to ISS (Istituto Superiore di Sanità), national reference laboratory in Rome, for agglutination tests with O1 and O139 antisera and resulted negative. Antibacterial susceptibility screening to antibiotics was conducted in our laboratory using the gradient test method (Etest strip), and the results were interpreted according to guidelines from the European Committee on Antimicrobial Susceptibility Testing (EUCAST). The bacterium was sensitive to piperacillin/tazobactam, cefotaxime and ceftazidime, fluoroquinolones, meropenem, azithromycin and cotrimoxazole, while susceptibility to doxycycline could not be tested due to unavailability of Etest strip. Therefore, two days after the start of antibiotic therapy, intravenous ciprofloxacin was added to the ongoing therapy. However, due to poor venous access limiting the prolonged administration of piperacillin/tazobactam, the radiological signs of cholangitis requiring an appropriate therapy but gastrointestinal symptoms limiting the possibility of potentially tolerating metronidazole in combination with a cephalosporin, on the third day of antibiotic therapy, it was shifted to oral ciprofloxacin and ertapenem. After an initial onset of diarrhoea in the first days of hospitalization, clinical evolution was favourable, with a rapid decrease in fever, blood pressure stabilization, bowel normalization and resolution of abdominal pain after five days. Follow-up blood cultures were taken on the second and fifth days of antibiotic treatment and resulted negative. In addition, an abdominal ultrasound documented the resolution of common bile duct thickening. The patient was then discharged in good general condition after 15 days of antimicrobial therapy.

Conclusion

NOVC infections have not been linked to epidemics, but systemic and several infections with bacteraemia have increased in recent years due to ongoing global warming, anthropisation of coastal environments, international seafood trade, consumption of undercooked seafood, an aging population, and a growing number of susceptible hosts in the world population. Physicians should maintain a high index of suspicion for this pathogen when evaluating ill patients with risk factors such as diabetes mellitus, chronic liver disease or malignancies, a history of seafood ingestion or marine exposure, and symptoms like fever, diarrhoea, and abdominal pain, in order to intervene as soon as possible. In this context, rapid preliminary laboratory data, such as rapid identification by MALDI-TOF MS and antimicrobial susceptibility testing, performed following short-term incubation cultures, may improve clinical outcome and guide the physicians towards the best therapy. Furthermore, Scientific Literature shows significant heterogeneity in antimicrobial strategies. Ciprofloxacin appears to be an appropriate targeted therapeutic option for NOVC bacteraemia. Also, dual-agent therapies (combining a third-generation cephalosporin with a tetracycline or fluoroquinolone) have been recommended in light of increasing antimicrobial resistance. In conclusion, further studies are required to define the optimal management and therapy of NOVC bacteraemia.

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