Bacteremia Caused by Arcobacter butzleri in an Immunocompromised Host

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Arcobacter butzleri is an emerging pathogen that has been implicated as the causative agent of persistent watery diarrhea. We describe a case involving a patient with chronic lymphocytic leukemia who developed invasive A. butzleri bacteremia. This case illustrates the unique challenges involved in diagnosing infections caused by emerging gastrointestinal pathogens.

CASE REPORT

An 85-year-old man presented to our institution with fever, hypotension, and chronic, persistent diarrhea that had begun during a return flight to the United States from a European cruise 4 weeks prior to presentation. His medical history was significant for chronic lymphocytic leukemia (CLL), classified as Rai stage 0, that was diagnosed in 2009. The patient began idelalisib monotherapy in November 2013 due to progression of his CLL to Rai stage III.

The patient was admitted approximately 6 months (July 24th) after beginning treatment and was hypotensive (81/53 mm Hg), tachycardic (heart rate, 118 beats per min), and febrile (39.3°C). The patient was found to be dehydrated, had explosive diarrhea 3 or 4 times per day, and was taking furosemide for edema of the lower extremities. On examination, the patient appeared ill, his abdomen had normal bowel sounds, and he did not display guarding or rigidity. His skin exam was remarkable for a diffuse maculopapular rash and chronic bilateral edema of the lower extremities above the knee, and he had open, weeping, serous wounds in the right lower extremity.

The patient’s complete blood count was remarkable for leukocytosis (chronic from CLL); he had a white blood cell count of 35,200/µl (normal = 4,000 to 11,000/µl), hemoglobin of 11.2 g/dl (normal = 13 to 17 g/dl), hematocrit of 31.7% (normal = 38 to 52%), and 196,000 platelets/µl (normal = 160,000 to 400,000/µl). A peripheral blood smear revealed anisocytosis and smudge cells, consistent with his diagnosis of CLL. The chemistry labs were remarkable for hypokalemia (potassium, 2.5 mEq/liter [normal = 3.5 to 5.1 mEq/liter]). Stool samples were sent to the microbiology laboratory for further analysis. Testing performed on the stool specimen included a Clostridium difficile PCR (Cepheid Inc., Sunnyvale, CA) and a gastrointestinal PCR panel (Luminex Corp., Toronto, Canada) which includes the following targets: norovirus group I/II, rotavirus A, Campylobacter spp., Escherichia coli O157, enterotoxigenic E. coli (ETEC), Salmonella spp., Shiga toxin-producing E. coli (STEIC), Shigella spp., Cryptosporidium spp., and Giardia lamblia. Both the C. difficile PCR and the gastrointestinal panel were negative.

Two blood culture sets were drawn daily during the first 5 days of hospitalization (BD Bactec; Becton Dickinson and Company, Franklin Lakes, NJ), and the first anaerobic bottle collected turned positive after 23 h of incubation. The Gram stain of the positive anaerobic blood culture revealed curved, Gram-negative rods (Fig. 1A). The aerobic blood culture bottles remained negative. The anaerobic blood culture was subcultured to MacConkey, chocolate, colistin nalidixic acid (CNA), and chopped meat carbohydrate media, which were incubated aerobically at 37°C with 5% CO2. In addition, the blood culture was subcultured onto anaerobic blood and phenylethyl alcohol (PEA) agars, which were incubated under anaerobic conditions at 37°C. Given the morphological characteristics similar to those of Campylobacter jejuni, the anaerobic blood bottle was also subcultured onto Campy CVA agar, which was incubated at 42°C in a sealed container with GasPak EZ Campy container system sachets (Becton Dickinson and Company, Franklin Lakes, NJ). Growth was observed on chocolate agar only after 2 days. A Gram-negative MIC MicroScan panel (Siemens Healthcare Diagnostics, Inc., Tarrytown, NY) was set up to determine identification and antimicrobial sensitivities; however, the organism did not grow in this platform and was not identified. Because the organism did not grow on the Mueller-Hinton agar or in the MicroScan panel, we were unable to perform antimicrobial susceptibility testing. The isolate also was also tested by matrix-assisted laser-detected ionization—time of flight mass spectrometry (MALDI-TOF MS) (Vitek MS, v2.0 knowledge base; bioMérieux, Durham, NC) but again was not identified. Finally, the isolate was sent to Mayo Medical Laboratories (Rochester, MN) for identification by 16S rRNA sequencing (MicroSeq ID; Applied Biosystems) and identified as Arcobacter butzleri (100% match to SmartGene accession no. AP012047).

Idelalisib was discontinued in July 2014 due to concerns regarding idelalisib-associated lymphocytic colitis, cellulitis, rash, and bacteremia. The hypotension resolved with 2 liters of normal saline, and the patient was empirically treated with vancomycin
Arcobacter skirrowii

Campylobacter

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day, and the bacteremia resolved by the third day. The patient was
discharged in stable condition after 14 days. The prolonged hospitalization was due to the patient awaiting placement in subacute rehabilitation giving deconditioning.

Arcobacter spp. are Gram-negative, spiral-shaped, non-spore-

forming organisms belonging to the family Campylobacteraceae

(Fig. 1B) (1). Arcobacter spp. were previously described as atypical or aerotolerant Campylobacter spp. (2); however, the genus was formally proposed in 1991 (3). At present, the Arcobacter genus contains 20 different species identified from environmental, animal, and human sources, of which three have been implicated in human disease: Arcobacter butzleri, Arcobacter cryaerophilus, and Arcobacter skirrowii (4–6). Optimal growth occurs at 30°C under microaerobic conditions, with a respiratory type of metabolism,

although growth is possible under aerobic conditions at temperatures ranging from 15°C to 37°C (1). In general, Arcobacter can be differentiated from Campylobacter by its optimal growth at lower temperatures and aerotolerance.

Relatively little is known about the global contribution of Arcobacter spp. to human health (7). These organisms have been isolated from the intestines of healthy dairy cattle, pigs, sheep, and horses but have more commonly been isolated from poultry, suggesting that poultry might be a major reservoir for the organism (8–10). Relatively little is known about the epidemiology, pathogenesis, and clinical significance of Arcobacter, but it is thought that this organism is transmitted via consumption of contaminated food or water (11–13).

Several case reports in the literature have implicated Arcobacter as the causative agent of abdominal cramps and persistent, watery diarrhea. In 1991, Taylor et al. described Arcobacter (previously atypical Campylobacter) as the third most common isolated organism from diarrheic stools collected from 631 children in Bangkok, Thailand (14). In 1983, an outbreak of A. butzleri occurred in 10 children at a nursery and primary school in Italy. In this outbreak, none of the children had diarrhea, but all of them reported abdominal cramps. Arcobacter butzleri was isolated from the stool of all affected children and identified by DNA-DNA hybridization (15). Arcobacter butzleri was the fourth most common Campylobacter-like organism isolated from patients with diarrhea in Belgium (2004) and France (2006) (7,16,17). Prouzet-Mauleon et al. stated that patients with A. butzleri presented with clinical features similar to those seen with Campylobacter infection but more commonly reported a persistent watery diarrhea rather than bloody diarrhea (16). In Turkey, A. butzleri was identified as a cause of gastroenteritis, at a rate of 0.3% in 3,297 stools examined. In that study, one third of the patients with A. butzleri infections presented with diarrhea, and all of them presented with abdominal pain and nausea (18). Arcobacter butzleri has also been detected in travelers’ diarrhea at a rate of 8% (16/201 stool specimens) in U.S. and European travelers returning from Mexico, Guatemala, and India (19). However, in that study, other organisms were also concomitantly isolated from stool samples from 13 of these patients, confounding the role of Arcobacter as the causative agent of the symptoms in these patients (19). A. butzleri has also been implicated in severe and persistent diarrhea in immunocompromised adults (16).

In our review of the literature, we found only three published case reports of A. butzleri bacteremia. A case of A. butzleri bacteremia was described in a 60-year-old male in Taiwan with liver cirrhosis, fever, and esophageal variceal bleeding (20). In Hong Kong, a 69-year-old female with appendicitis and local perforation developed A. butzleri bacteremia (18). In 1995, a case report from London described a neonate with bacteremia, suggesting possible vertical transmission of this organism (21). In all of these cases, the patients received antibiotics and the bacteremia resolved (22). The patient described here reported having diarrhea for 4 weeks prior to admission. During that time, he was screened for C. difficile by PCR on two occasions, and both screenings were negative. The diarrhea was considered a side effect of the idelalisib therapy (23), so the patient was taken off the medication, 10 days prior to admission, but diarrhea persisted. No further workup was done at that time. At the time the patient had first presented, he had arrived from a European cruise. Given that the patient started to have diarrhea while he was on the airplane, we suspect that he

FIG 1 Gram stain morphology of Arcobacter butzleri from the blood culture bottles (A) and from the colony (B). Curved cells are indicated by black arrows. Scale bars, 10 μm.
acquired the infection while he was abroad. Because our institution does not perform stool culture, we could not recover *A. butzleri* from the patient’s stool samples. Our suspicion is that *A. butzleri* was indeed the cause of his diarrhea and that his immunocompromised status (CLL) facilitated the severe and chronic diarrhea and the ensuing bacteremia. The patient was started on empirical broad-spectrum antibiotics (vancomycin and piperacillin-tazobactam) at the time of admission, and his bacteremia resolved by the second day and the bacteremia by the third day. It is unclear if antibiotics contributed to the patient’s improvement or if the infection could have been cleared by itself; however, given that the patient had severe symptoms for 4 weeks prior to starting antibiotics and that the symptoms resolved after the antibiotic treatment, we suspect that the antibiotics led to an improvement in this patient’s condition. These events are consistent with the previously published bacteremia case reports where the patients’ symptoms resolved after antibiotic treatment.

Identifying gastrointestinal (GI) pathogens is a continuous challenge for clinical microbiology laboratories (24). Conventional diagnostic procedures include procedures such as enrichment steps, use of selective culture media, biochemical identification, serotyping, and antimicrobial susceptibility testing. These methods are laborious and time-consuming, with final results being obtained only after 3 or 4 days. Further, the limited viability of some enteric pathogens (i.e., *Shigella*) limits their detection by culture-based methods (25–27). Implementation of molecular-detection panels for common GI pathogens has increased the detection of these pathogens in stool (28). However, molecular methods are limited by the targets available in these panels (29). Despite evidence that *A. butzleri* is an emerging, clinically relevant organism, specimens are not routinely tested for *Arcobacter* spp. (9). Furthermore, movement away from traditional stool culture and toward targeted, molecular-technique-based diagnostic panels further limits our ability to detect these emerging pathogens. The significance and prevalence of *Arcobacter* in human infections have, therefore, likely been underestimated because of inappropriate detection and typing methods used with stool samples (9). In the case presented here, the organism was identified because of the bacteremia; we were unable to identify the organism in the stool samples with methods currently used in our laboratory. It should be noted that the *A. butzleri* isolate was not identified by MALDI-TOF MS (Vitek MS, v2.0 knowledge base; bioMérieux, Durham, NC) in our laboratory because this organism is not included in the bioMérieux database; however, subsequent testing on the Bruker MALDI-TOF MS successfully identified the organism (identification score = 2.004; Biotype version 3.1).

Finally, the 16S rRNA sequencing platform (MicroSeq ID; Applied Biosystems) was sufficient to successfully identify the pathogen with 100% homology to *Arcobacter butzleri*. The sequence also had similarity to *Arcobacter cryaerophilus* and *Campylobacter curvus*, but with reduced agreements at 97.8% and 83.5%, respectively. In conclusion, invasive disease by *Arcobacter butzleri* in immunocompromised individuals could become life-threatening. Clinical microbiology laboratories and clinicians should be aware of this organism and its potential for invasive disease, particularly in cases where patients present with persistent watery diarrhea.

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**REFERENCES**


