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CASE REPORT

Association of *Campylobacter upsaliensis* with Persistent Bloody Diarrhea

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***Campylobacter upsaliensis* is a zoonotic, emerging pathogen that is not readily recovered in traditional stool culture. This case represents the first report of persistent bloody diarrhea with *C. upsaliensis* that was confirmed by filtration culture, PCR, and sequencing.**

CASE REPORT

An 83-year-old male presented to the emergency department (ED) with an acute history of severe bloody diarrhea. His symptoms began with nausea, vomiting, and abdominal cramping, which he mistook for constipation. The patient took a single dose of laxative and shortly thereafter experienced numerous episodes of profuse bloody diarrhea that continued for several hours. He did not have fevers, chills, or sweats. The patient was found by his wife at home, collapsed in a chair, and was brought to the ED for evaluation. The patient's past medical history was significant for irritable bowel syndrome but no history of bloody diarrhea or rectal bleeding. His social history revealed contact with his sister-in-law and two canine pets, all with bloody diarrhea. On arrival in the ED, the patient's physical examination was unremarkable; however, out of concern for a lower gastrointestinal bleed, the patient was admitted for observation and further testing. Stool studies were negative for all gastrointestinal pathogens, including *Salmonella*, *Shigella*, *Campylobacter*, *Aeromonas*, *Plesiomonas*, and *Vibrio* by stool culture, *Cryptosporidium*, *Giardia*, and Shiga-toxigenic *Escherichia coli* (STEC) by enzyme immunoassay (EIA), and *Clostridium difficile* by PCR. In addition, ovum and parasite exams of the stool were performed and were remarkable only for numerous erythrocytes and leukocytes. These findings were consistent with the grossly bloody stool and a positive fecal lactoferrin EIA. The patient's symptoms gradually improved but did not resolve over the course of 48 h. He remained afebrile and hemodynamically stable and was discharged on hospital day 2 with no known etiologic cause of diarrhea. Five days later, he was treated with ciprofloxacin for continuing diarrhea out of concern for possible person-to-person spread of a still-unidentified gastrointestinal pathogen but only after STEC was ruled out by Shiga toxin EIA.

The clinical microbiology laboratory was consulted for additional testing for enteroinvasive or enteroaggregative *E. coli*, given the widely publicized enteroaggregative/Shiga-toxigenic *E. coli* O104:H4 outbreak that had recently concluded in Germany. No testing was available for these organisms; however, the stool was filtered through a 0.6-μm filter (Pall Life Sciences, Ann Arbor, MI) onto a brucella blood agar plate (Hardy Diagnostics, Santa Maria, CA) and cultured in an increased-hydrogen atmosphere of approximately 6.5 to 12.5% (7) (BioBag Type Cfj; BD, Franklin Lakes, NJ) at 37°C to enhance the detection of hydrogen-requiring *Campylobacter* spp. (21). For direct stool PCR, the specimen was treated with AL stool lysis buffer (Qiagen, Valencia, CA) and heated at 95°C for 10 min. The DNA was extracted with the Maxwell Cell LEV DNA purification kit on a Maxwell 16 automated extraction platform (Promega, Madison, WI). The PCR targeted a conserved region of the *Campylobacter* 16S rRNA gene and was positive (22). The amplified gene product was then sequenced, with a sequence 100% identical to that of *Campylobacter upsaliensis*. The subsequent filter culture grew small glistening colonies at 72 h of incubation that were weakly oxidase-positive, catalase-negative, Gram-negative "gull-shaped" rods (Fig. 1A and B). 16S rRNA sequencing was then performed on the colonies, and the result was also 100% identical to the sequence of *C. upsaliensis* (1,119-bp identity). The isolate had low MIC values for quinolones and macrolides (Table 1) (6). Retrospective stool specimens from the sister-in-law and both dogs (collected >3 weeks after the patient's admission) were tested by filtration culture and PCR. All specimens were culture negative. The sister-in-law was positive by PCR for the *Campylobacter* genus (22); however, the species could not be definitively determined by 16S rRNA sequencing.

Campylobacter upsaliensis has been isolated from human blood, placental tissue, breast abscess, and stool (8, 13, 20, 25). There have also been rare/controversial reports of hemolytic-uremic syndrome and Guillain-Barré syndrome associated with *C. upsaliensis* (4, 9, 14). In both pediatric and immunocompromised hosts, *C. upsaliensis* is recognized as a clinically important emerging diarrheal pathogen (10, 17, 19). However, human cases of *C. upsaliensis* gastroenteritis with severe persistent bloody diarrhea similar to that observed in this patient have not been described. It is unclear what role treatment plays in recovery from these infections, and limited data are available for antibiotic resistance rates in *C. upsaliensis.* In several studies, erythromycin resistance has ranged from 10 to 15% for *C. upsaliensis* (11, 25, 28). Ciprofloxacin resistance in one study was approximately 5%, and resistance to quinolones in *C. upsaliensis* has been associated with prior pa-

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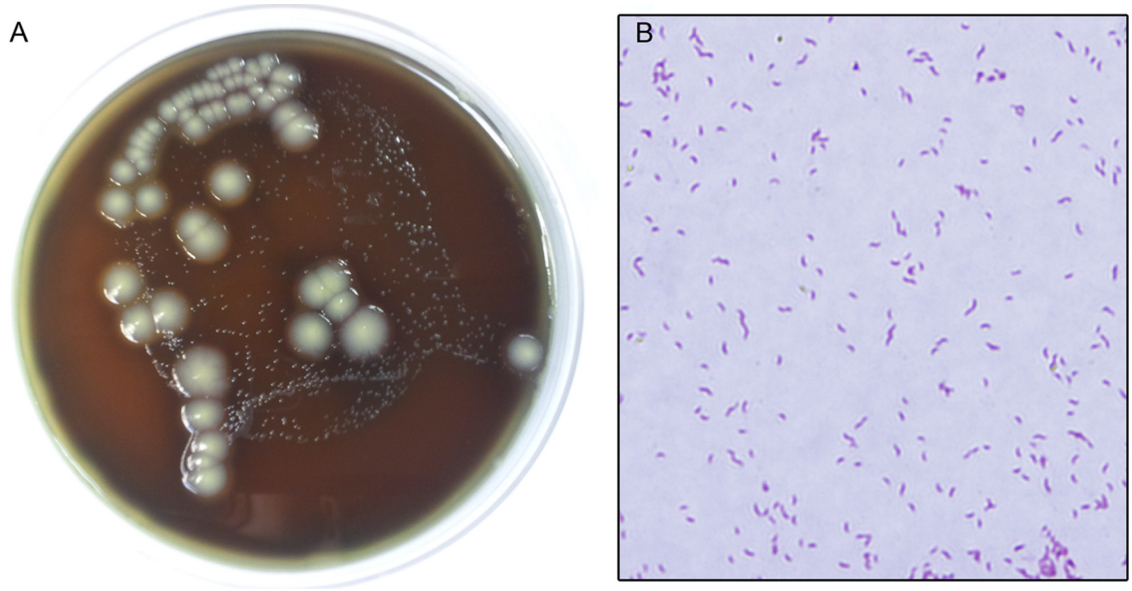

FIG 1 Filter culture of the patient's stool sample. Small glistening colonies were identified as *Campylobacter upsaliensis* and grew in 72 h (A). The characteristic Gram stain morphology for *C. upsaliensis* is seen in panel B. Large white creamy colonies stained as Gram-positive rods, grew in less than 24 h, are regularly seen on *Campylobacter*-negative cultures, and were not consistent with *Campylobacter* (A).

tient exposure to quinolones in the setting of chronic unresolved diarrhea (17, 28). The rate of quinolone resistance for *C. upsaliensis* is low compared to those for *Campylobacter jejuni* and *Campylobacter coli*, which have surpassed 40% (23). This likely reflects the fact that *C. coli* and *C. jejuni* have been regularly exposed to sarafloxacin and enrofloxacin in the poultry industry, whereas domestic felines and canines (the reservoir for *C. upsaliensis*) would not have similar exposure to drive resistance (24).

The source of this infection could not be determined in this investigation, since only the patient was culture and PCR positive. *C. upsaliensis* is a well-documented cause of diarrhea in felines and canines. Therefore, one hypothesis is that the symptomatic dogs transmitted this infection to the patients (3, 26). Reports of serious infections attributed to pet-to-human transmission from both cats and dogs have been documented (12, 13). We were unable to detect *C. upsaliensis* in either dog's stool >3 weeks after symptoms; however, identification of *C. upsaliensis* in the dogs' stool would not have been definitive evidence of a point source, because up to 58% of nondiarrheic dogs are thought to be transiently colonized with *C. upsaliensis* (5). An alternative hypothesis is that the sister-in-law (who had molecular evidence of recent infection with a *Campylobacter* species and was treated empirically) may have acquired *Campylobacter* by drinking unfiltered spring water while recently hiking and subsequently transmitted the infection to the patient while visiting his home during her illness. Acquisition of *C. jejuni* from drinking contaminated groundwater has been previously described for hikers (27), and human-to-human transmission of both *C. upsaliensis* and *C. jejuni* have been described (10, 18). It is also possible that the patient acquired the infection from a source unrelated to the canines' or sister-in-law's illnesses.

TABLE 1 Antimicrobial susceptibility profile of *C. upsaliensis* isolated from the patient's stool by filtration culture[a]

Drug	MIC(s) (μg/ml)
Ampicillin-sulbactam	1, 0.5
Amoxacillin-clavulanate	0.5, 0.25
Cefoxitin	16
Trimethoprim-sulfamethoxasole	>2, 38
Ceftriaxone	16
Meropenem	<0.25
Clindamycin	1
Ampicillin	2
Moxifloxacin	<0.06
Piperacillin-tazobactam	32, 4
Metronidazole	8
Vancomycin	>8
Penicillin	>2
Nitrofurantoin	>8
Tetracycline	0.5
Azithromycin	<0.25

[a] MICs were obtained by broth microdilution performed according to CLSI standards for *C. jejuni/C. coli* (6).

The routine work-up for stool culture performed in most clinical labs in the United States does not include nonselective *Campylobacter* culture, such as the procedure that was performed in this study (15). While many *Campylobacter* species may "break through" the conditions optimized for *C. jejuni* and *C. coli* in a standard *Campylobacter* culture (i.e., 42°C incubation, cephalosporin-containing selective media, microaerobic environment, and culture discard at 72 h), many species of *Campylobacter* cannot tolerate one or more of these restrictive conditions. In particular, *C. upsaliensis* is typically sensitive to cephalosporins, thrives in an increased-hydrogen atmosphere, and typically grows in 96 h or more. Goossens et al. (11) found that of 99 *C. upsaliensis* isolates obtained by filtration culture, only 4 grew in a standard selective *Campylobacter* culture. This patient's routine *Campylobacter* culture was plated on cephalosporin-containing medium and incubated in a hydrogen-deficient atmosphere (Mitsubishi

AnaeroPouch-MicroAero; Remel, Lenexa, KS), and the plates were discarded after 72 h, likely accounting for the lack of organism recovery. Use of similar conditions may account for an underappreciation of this species as a gastrointestinal pathogen. Studies in South Africa using filtration culture have found *C. upsaliensis* accounting for 23% of *Campylobacter* stool isolates (19), whereas Irish and Canadian studies using filtration culture and/or PCR detected *C. upsaliensis* in only 0.7 to 2.1% of stool specimens (1, 2, 16). These data suggest that the prevalence of this species may be geographically variable. Importantly, filtration culture and direct stool PCR/sequencing for the *Campylobacter* genus are not routinely available to most laboratories.

This report draws attention to the clinical importance of *C. upsaliensis* and reveals an emerging pathogen, capable of causing severe persistent bloody diarrhea. In this patient, the etiological agent of this infection would not have been identified were filtration culture and PCR not employed. The approach taken in this case also argues for the use of alternative methodologies amenable to the detection of other clinically relevant *Campylobacter* species that are intolerant to routine selective culture conditions.

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