Helicobacter canis Bacteremia in a Patient with Fever of Unknown Origin

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A 57-year-old woman with common variable immunodeficiency and liver failure of unknown etiology presented with recurrent fevers over a 5-month period. She was found to have Helicobacter canis bacteremia. Immunocompromised hosts with exposure to cats or dogs may be at risk for infection with this organism, which may be challenging to diagnose.

CASE REPORT

A 57-year-old woman from Montana was referred to our institution for Infectious Diseases consultation for recurrent fever and chills for 3 months. She had common variable immunodeficiency (for which she received intermittent intravenous immune globulin infusions), and presumed pulmonary sarcoidosis (treated intermittently with prednisone), and had undergone prior splenectomy. She had a 2-year history of elevated alkaline phosphatase. She had developed intermittent fever 3 months prior to consultation and had been previously hospitalized locally for fever and clinical sepsis with negative blood cultures. Laparoscopic liver biopsy had shown mildly active steatohepatitis with periportal fibrosis, and had been procedurally complicated by intra-abdominal hemorrhage. She had been hospitalized for fever on several subsequent occasions and had received multiple courses of empirical antibacterial therapy despite negative blood cultures and no clear definition of an infectious process.

Upon presentation for initial Infectious Diseases consultation, fevers were described as low grade and intermittent and were accompanied by chills and sweats. She had taken prednisone (20 mg daily) for the previous 3 months for abdominal pain ascribed to possible gastrointestinal sarcoidosis. She reported a 1-year history of diarrhea and a 2-year 160-pound weight loss. A colonoscopic biopsy 5 months prior had shown findings consistent with common variable immunodeficiency. Stool studies showed no evidence of enteric infection. She had two dogs and three cats. The patient’s blood cultures, serologic testing for HIV, blood PCR for cytomegalovirus, and chest X-ray were negative. Serum IgG was 408 mg/dl (767 to 1,590 mg/dl), and IgA was 2 mg/dl (61 to 356 mg/dl). Total bilirubin was 0.4 mg/dl (0.1 to 1 mg/dl), alkaline phosphatase 566 units/liter (46 to 118 units/liter), and alanine transaminase 155 units/liter (7 to 45 units/liter). She was subsequently transferred to our hospital, at which time she was afebrile in the absence of having received antimicrobial therapy. Blood cultures were negative. An evaluation was initiated for possible liver transplantation. Magnetic resonance cholangiopancreatography showed no evidence for cholangitis or biliary obstruction. Computed tomography of the abdomen revealed a large fluid collection around the distal stomach, which was percutaneously drained. A Gram stain and cultures of the fluid were negative. Bone marrow cultures for bacteria, mycobacteria, and fungi and urine Histoplasma antigen were negative.

A week after hospitalization at our institution, she developed fever to 39.3°C and two sets of blood cultures were obtained (results below). Chest imaging showed bibasilar infiltrates, and a sputum culture grew Escherichia coli, prompting empirical treatment with meropenem for 8 days. A liver biopsy again showed an indeterminate pattern of portal tract inflammation, fibrosis, and severe cholestasis; cultures of liver biopsy tissue were not performed.

Two sets of two Bactec Plus Aerobic/F culture bottles and one Bactec Plus Anaerobic/F culture bottle (Becton, Dickinson Diagnostic Systems, Sparks, MD) were incubated on Bactec 9240 instruments (Becton, Dickinson). One aerobic bottle signaled positive after 90 h, and the second aerobic bottle from the same set signaled positive at 93 h. The two aerobic bottles from the second set signaled positive at 104 h. No organisms were observed on Gram stain examination of blood culture bottle contents; however, an acidine orange stain revealed rod-like organisms. An organism was isolated after 48 to 72 h of subculture; it grew as a thin, oily film (Fig. 1a) on chocolate blood agar under microaerophilic conditions at 37 and 42°C, growing optimally at 42°C. Gram staining of the colonies revealed Gram-negative spiral-shaped rods (Fig. 1b). The organism hydrolyzed indoxyl acetate, was urease and catalase negative, and failed to reduce nitrate to nitrite or NH3 gas. A total of 1,376 bp of the 16S rRNA gene was sequenced (MicroSeq Full Gene 16S rDNA PCR and sequencing kits; Applied Biosystems, Carlsbad, CA). The generated sequence was 99.3%
Helicobacter canis is a zoonotic pathogen that may colonize the mucosal surfaces of the intestinal tract and/or liver. It is bile tolerant, fecal source, and can grow at 42 and 37°C. It is catalase, urease, and nitrate negative but positive for gamma glutamyl transpeptidase, alkaline phosphatase, and indoxyl acetate. DNA-DNA hybridization and 16S rRNA gene sequencing show it to be a distinct species from Helicobacter hepaticus. Its bile tolerance, fecal source, and absence of urease activity may explain colonization of the lower intestinal rather than gastric mucosa.

Our patient’s immune deficiency presumably placed her at risk for infection with H. canis. She had exposure to dogs and cats; as H. canis may colonize the colon of either (15,17), we hypothesize that she acquired H. canis infection from a pet. Gerrard et al. described the clinical picture of recurrent episodes of fever over a 10-month period and bacteremia with Helicobacter-like organisms (including H. canis) in a patient with X-linked agammaglobulinemia (4). The relapsing infection occurred despite repeated courses of antibiotics, with cure achieved only after administration of 5 months of oral doxycycline and metronidazole. Persistent H. canis bacteremia has also been described in a patient with gastric lymphoma receiving chemotherapy (12). Our patient had recurrent episodes of fever. Given the possibility for relapse with a short course of therapy, we elected to treat our patient for a prolonged duration. At the time of telephone follow-up 20 weeks after completing therapy, she did not report recurrent fever.

Recognition of H. canis infection is challenging since the organism may fail to grow in primary culture or subculture. Since it is relatively inert biochemically, sequencing is frequently required for identification (1). There are no guidelines from the Clinical and Laboratory Standards Institute for methods or breakpoints to assess antimicrobial susceptibility of H. canis. MICs of 20 antimicrobial agents for 43 and 6 isolates of Helicobacter cinaedi and Helicobacter fennelliae, respectively, were determined by Flores et al. by agar dilution (18). Antibiotics that were active in vitro against all tested isolates were ampicillin, gentamicin, doxycycline, tetracycline, chloramphenicol, nalidixic acid, rifampin, and ceftriaxone. Leeman et al. suggested that in vitro susceptibility of H. canis may not correlate with clinical response (14), and no published data exist regarding susceptibility testing and therapeutic recommendations for H. canis. The best-studied non-pylori Helicobacter species is H. cinaedi, and even for this species, an optimal regimen and duration of therapy are unknown. Solnick et al. suggest doxycycline for patients who are not acutely ill, and cluding cholecystitis, hepatitis, and possibly hepatic cancer (6), and have been detected in livers of patients with ulcerative colitis and concomitant liver disease, as well as in children with other liver diseases (7,8).

H. canis was first described in 1993 in feces of dogs with and without diarrhea (9). It resembles Helicobacter hepaticus, is bile tolerant, and can grow at 42 and 37°C. It is catalase, urease, and nitrate negative but positive for gamma glutamyl transpeptidase, alkaline phosphatase, and indoxyl acetate (10). DNA-DNA hybridization and 16S rRNA gene sequencing show it to be a distinct species from H. hepaticus (11). Its bile tolerance, fecal source, and absence of urease activity may explain colonization of the lower intestinal rather than gastric mucosa (12).

There have been six reported human infections with H. canis (4, 12–16). The first was a 1993 case report of a boy with gastroenteritis (13), followed by four reports of H. canis bacteremia (4, 12, 14, 15). Bacteremia was associated with multifocal cellulitis in two cases (a patient with X-linked agammaglobulinemia and an immunocompetent patient (4, 14)), while in the other two cases (an otherwise healthy infant and a 78 year old receiving chemotherapy for lymphoma (12, 15)), cellulitis was not a feature. The most recently published case reports H. canis in chronic duodenal ulcerations in a patient with Crohn’s disease (16). Close contact with either dogs or cats was reported in all cases. Dogs are an important reservoir for this infection, being the animal most commonly reported in exposure of infected humans (four of six cases).

Human Helicobacter infections are typically due to Helicobacter pylori. Non-pylori Helicobacter species (including H. canis) that colonize the mucosal surfaces of the intestinal tract and/or liver are mostly zoonotic pathogens of mammals or birds, infrequently reported to cause invasive infection in humans (1). Especially susceptible are humans with immunodeficiencies such as AIDS (2) and X-agammaglobulinemia (3–5). These organisms may be associated with diarrhea, bacteremia, and/or visceral disease, including cholecystitis, hepatitis, and possibly hepatic cancer (6), and have been detected in livers of patients with ulcerative colitis and concomitant liver disease, as well as in children with other liver diseases (7,8).

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imipenem or ceftriaxone plus gentamicin for those who are more ill, including those with bacteremia. A minimum of 2 weeks of therapy is suggested, with longer durations for bacteremia or serious illness

For patients presenting with fever of unknown origin, the possibility of H. canis infection should be considered, particularly in those with exposure to dogs or cats.

**Nucleotide sequence accession number.** The sequence generated in this work is available under GenBank accession no. KC293823.

**ACKNOWLEDGMENT**

We thank the outstanding staff of the Mayo Clinic Clinical Bacteriology Laboratory for their assistance with this challenging case.

**REFERENCES**