

## When Nature Meets Nurture: Persistent *Yersinia* Infection

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### PRESENTATION

When the patient's symptoms are alleviated, it might seem that the causative infection has cleared. But that was not the case for a 62-year-old man with type 2 diabetes who presented with a 1-week history of constipation, lower abdominal cramping, rectal pressure, and hematochezia. In the emergency department, laboratory testing detected leukocytosis with a white blood cell count of  $19 \times 10^3$  cells/mm<sup>3</sup> and an elevated neutrophil count.

Computed tomography (CT) of the patient's abdomen and pelvis demonstrated marked inflammation of the rectal wall. He was admitted and underwent colonoscopy, which confirmed the presence of proctitis but was otherwise normal. Four days after admission, his stool culture grew pan-sensitive *Yersinia enterocolitica*. A diagnosis of *Yersinia* proctitis was made. Simple hepatic cysts seen on CT were felt to be incidental. The patient was prescribed a 5-day course of oral ciprofloxacin. He returned home and had complete symptom resolution.

However, 3 weeks after completing treatment, he experienced gradual onset of severe pain that began in the right upper quadrant of the abdomen and radiated to his back and right shoulder. This was accompanied by malaise, intermittent fevers, and anorexia. He reported a 21-pound unintentional weight loss over the preceding 2 months. One month after discharge, he returned to the emergency department.

### ASSESSMENT

The patient was in obvious pain. His temperature was 97.4° F (36.3° C), blood pressure was 164/107 mm Hg, and heart rate was 98 beats per minute. Palpation of the right upper quadrant elicited tenderness but no guarding or rebound;

bowel sounds were normal. He had no lymphadenopathy, caput madusae, or spider angiomas, and his sclerae were anicteric.

A complete blood count ordered on admission revealed leukocytosis with a white blood cell count of  $13 \times 10^3$  cells/mm<sup>3</sup>. Aside from a blood glucose measurement of 213 mg/dL, his metabolic profile was within normal limits. Other laboratory results were as follows: aspartate aminotransferase, 51 U/L; alanine aminotransferase, 39 U/L; alkaline phosphatase, 141 IU/L; and total bilirubin, 0.6 mg/dL. Blood cultures demonstrated *Y. enterocolitica*. Repeat CT of the abdomen and pelvis disclosed multiple irregular hypodense lesions in his liver, the largest of which was 4.5 cm in diameter (**Figure 1**). These corresponded to the locations of the "simple cysts" seen on the prior study. The patient underwent percutaneous aspiration of 2 of these liver lesions. Purulent material was recovered, and cultures grew *Y. enterocolitica*.

### DIAGNOSIS

At the time of admission, it was unclear how the patient first developed *Yersinia* proctitis. After reexamining his social history, we confirmed that, when not working as a long-haul truck driver, the patient lived with his wife and son in a rural area of Tennessee. While they did not have direct exposure to livestock, the family routinely obtained a portion of their drinking water from a spring in a cave behind their home (**Figure 2**). The drainage basin for this spring apparently included multiple cattle farms and former pig farms. A sample of the spring water was collected by staff from the Tennessee Departments of Health and Environment and Conservation. Culture analysis by the Tennessee Department of Health Laboratory Services yielded *Y. enterocolitica*, identifying the spring water as a potential causative exposure.

Given that his wife and son shared the exposure to the contaminated water but did not have infection, consideration was given to the existence of underlying conditions that might have put the patient at particular risk of invasive *Yersinia* infection. Because of concern for iron overload as

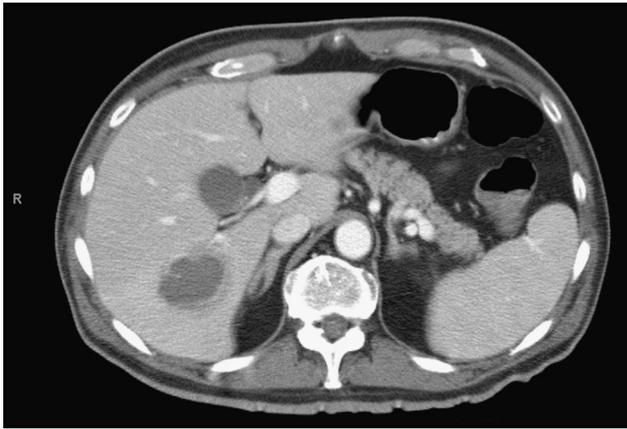
**Funding:** None.

**Conflict of Interest:** None.

**Authorship:** All authors had access to the data and a role in writing the manuscript.

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**Figure 1** Computed tomography showed multiple irregular hypodense lesions in the patient's liver. The largest was 4.5 cm in diameter.

a cause for this type of infection, a ferritin level was ordered and found to be above 4000 ng/mL. Genotyping for hemochromatosis was then sent. The results demonstrated H63D mutations in both alleles supporting a diagnosis of iron overload.

*Y. enterocolitica* is an enteropathogenic Gram-negative coccobacillus that can cause clinical syndromes ranging from self-limited enterocolitis to life-threatening systemic infection with metastatic manifestations. More than two-thirds of symptomatic patients present with fever, diarrhea, and abdominal pain that usually resolve without treatment. Among children and adolescents, *Y. enterocolitica* can produce mesenteric adenitis or terminal ileitis mimicking acute appendicitis and leading to unnecessary surgeries.<sup>1</sup> Although invasive disease is uncommon, it is associated with high mortality and often occurs in patients with immunosuppression or iron overload. In fact, underlying hemochromatosis was recognized in 64% of patients with hepatic abscesses caused by *Y. enterocolitica*.<sup>2</sup>



**Figure 2** Some of the family's drinking water came from a spring that was sheltered in a cave behind their home.

The organism causes less than 1% of foodborne illnesses in the US, with only 21 cases reported in Tennessee for 2010. Different serotypes can produce sporadic infections, whereas the highly virulent serotype O:8 is the most common strain isolated in outbreak settings.<sup>3</sup> Transmission of infection is fecal-oral, although infections via direct contact with infected animals or humans have been described. *Y. enterocolitica* has been isolated from contaminated foods, fresh water, and a variety of animal reservoirs including pigs, cows, sheep, goats, dogs, and birds. Infections transmitted by blood transfusion have resulted in sepsis and rapid death.<sup>4</sup> In our patient's case, the cave water was the most likely causative exposure. Comparison of the stool isolate with the spring water sample isolate by pulsed-field gel electrophoresis demonstrated different patterns. Water may be contaminated by multiple pathogenic strains, and nonmatching results do not rule out water as the probable source for this case.

The relationship between *Y. enterocolitica* septicemia and iron overload is well-established. Iron is a vital nutrient required for bacterial energy generation, DNA replication, and protection against oxidative stress. Pathogenic bacteria must obtain iron from host tissues in order to establish infection. One of the first lines of defense against bacterial infection in vertebrate hosts is the sequestration of nutrient iron. Most is stored intracellularly, within ferritin or within heme molecules, which serve as a cofactor to the protein portion of hemoglobin. The small proportion of iron present in the serum is tightly bound by circulating transferrin. Hemoglobin and free-circulating heme released through erythrocyte lysis are rapidly bound by haptoglobin and hemopexin, respectively.

In order to survive in a human host, bacteria must possess strategies to circumvent iron withholding. One of the most common ways by which pathogens accomplish this is by secretion of siderophores, which are low-molecular-weight complexes that have a higher binding affinity for iron than does transferrin. When iron supply is low, bacteria release siderophores, which out-compete transferrin for iron. Then, through recognition of bacterial cell-surface receptors, they carry the iron through the cell wall and cytoplasmic membrane, where it can be disengaged from the siderophore and used as fuel.<sup>5</sup>

The *Y. enterocolitica* serogroups O:3 and O:9 are the most common etiologies of *Yersinia* infections worldwide, but they are of relatively low virulence. Serogroup O:8, the major culprit in outbreaks, produces a siderophore (yersiniabactin) that can extract iron even in the iron-depleted environment of the serum. In contrast, serogroups O:3 and O:9 do not independently produce siderophores, and in normal hosts, their proliferation is largely restricted to the high-iron environment of the gastrointestinal tract.<sup>6</sup>

In patients who have an underlying iron-overload state, the weakly pathogenic serogroups may achieve a virulence equal to that of serogroup O:8, leading to septicemia and systemic infection. Thus, *Yersinia* septicemia has been associated with a wide variety of underlying disorders of iron overload including hemochromatosis, beta thalassemia, and sideroblastic anemia.<sup>7</sup> As illustrated by our patient's illness,

a new diagnosis of *Yersinia* septicemia should be considered an indicator of possible underlying iron overload.

## MANAGEMENT

Treatment for uncomplicated *Yersinia* enterocolitis is not routinely recommended, as it is usually a self-limited illness. In contrast, invasive disease with extraintestinal manifestations requires prompt antibiotic therapy. Commonly, *Y. enterocolitica* is susceptible to a wide variety of antimicrobials including trimethoprim-sulfamethoxazole, third-generation cephalosporins, aminoglycosides, quinolones, and tetracyclines.<sup>1</sup> Our patient underwent percutaneous drainage of liver abscesses with drains in place for 38 days. He received ceftriaxone, 2 gm intravenously (IV) daily for 50 days, reinforced with gentamicin, 120 mg IV every 12 hours, for 9 days. He was discharged on hospital day 11 with home healthcare services to assist in the administration of IV antibiotics at home.

Treatment continued with oral ciprofloxacin for 4 weeks after discontinuation of ceftriaxone. At this point, resolution of liver abscesses was proven on imaging, and treatment was discontinued. Repeat iron studies demonstrated mild iron overload without end-organ damage. The patient is now followed by a gastroenterologist, and he receives therapeutic phlebotomy as needed. He and his family received education on secondary prevention of infection and water purification.

At last contact, he was considering water treatment. Of note, no additional cases of *Y. enterocolitica* infection have been reported from this county.

## ACKNOWLEDGMENTS

We would like to thank Will Pride from the Tennessee Department of Environment and Conservation for his assistance with collecting samples and David E. Brumley, DDS, MPH, from the Tennessee Department of Health, who provided an important health consultation with the patient.

## References

1. Cover TL, Aber RC. *Yersinia enterocolitica*. *N Engl J Med*. 1989;321:16-24.
2. Bergmann TK, Vinding K, Hey H. Multiple hepatic abscesses due to *Yersinia enterocolitica* infection secondary to primary haemochromatosis. *Scand J Gastroenterol*. 2001;36:891-895.
3. Shayegani M, Morse D, DeForge I, Root T, Parsons LM, Maupin PS. Microbiology of a major foodborne outbreak of gastroenteritis caused by *Yersinia enterocolitica* serogroup O:8. *J Clin Microbiol*. 1983;17:35-40.
4. Bottone EJ. *Yersinia enterocolitica*: overview and epidemiologic correlates. *Microbes Infect*. 1999;1:323-333.
5. Skaar EP. The battle for iron between bacterial pathogens and their vertebrate hosts. *PLoS Pathog*. 2010;6:e1000949.
6. Chambers CE, Sokol PA. Comparison of siderophore production and utilization in pathogenic and environmental isolates of *Yersinia enterocolitica*. *J Clin Microbiol*. 1994;32:32-39.
7. Piroth L, Meyer P, Bielefeld P, Besancenot JF. *Yersinia* bacteremia and iron overload. *Rev Med Interne*. 1997;18:932-938.