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Listeria monocytogenes Cholecystitis: A Possible New Syndrome.

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Case Report.

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Listeria monocytogenes Cholecystitis: A Possible
New Syndrome

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Abstract: The U.S. Food and Drug Administration recently added potentially fatal *Listeria monocytogenes* infection to the list of opportunistic infections that can occur in patients who receive tumor necrosis factor inhibitor therapy. In this study, the first reported case of *L. monocytogenes* cholecystitis associated with etanercept use is described. It also appears that tumor necrosis factor inhibitor therapy likely increases the risk for *Listeria* cholecystitis. Clinicians need to be aware of this association when selecting antimicrobial therapy for these patients.

Key Indexing Terms: Cholecystitis; Tumor necrosis factor inhibitor;

Listeria monocytogenes is an important bacterial pathogen among patients at the extremes of age, women during pregnancy and individuals who are receiving immunosuppressive therapy and/or have impaired cell-mediated immunity. Central nervous system (CNS) infection and bacteremia are life-threatening manifestations of infection with this organism especially in immunosuppressed persons. A self-limited febrile gastroenteritis in immunocompetent hosts is also seen, but biliary tract infections such as cholecystitis are rare. To date, only 5 cases of *L. monocytogenes* cholecystitis have been reported in the medical literature.^{1–3} Two of the cases and our case occurred in patients with rheumatoid arthritis being treated with tumor necrosis factor inhibitor therapy (TNFIT). We postulate that TNFIT is likely a distinct risk factor for this entity and physicians who treat patients with biliary tract disease need to be aware of this association so that they may suspect the diagnosis and select an appropriate antimicrobial agent in addition to surgical therapy.

Case Report

A 56-year-old African American male presented to the

emergency department with right upper quadrant pain and jaundice. He had a medical history of alcoholic cirrhosis with minimal ascites and rheumatoid arthritis. He was receiving etanercept at a dosage of 25 mg/kg twice weekly for the preceding 5 years without infectious complications. He was an active alcohol user and smoker for years. He also reported frequent consumption of cheeses and other dairy products. On examination, he was icteric but afebrile. His heart rate was 105 beats per minute and blood pressure 136/70 mm Hg. An examination of the abdomen revealed evidence of ascites and tenderness in the right upper quadrant. Murphy's sign was absent.

Laboratory studies revealed a hemoglobin level of 11.5 g/dL, a white blood cell count of 16.3×10^9 cells per liter with 85% neutrophils and a platelet count of 102 cells per nanoliter. The aspartate aminotransferase level was 73 U/L, alanine aminotransferase level 38 U/L, alkaline phosphatase level 127 U/L and total bilirubin level 9.2 mg/dL. An abdominal ultrasound revealed a distended and thickened gallbladder with an 8-mm gallstone. Hepatobiliary iminodiacetic acid scan findings were compatible with acute cholecystitis. The patient underwent laparoscopic cholecystectomy without complication. The pathology of the gallbladder confirmed the diagnosis of cholecystitis. Perioperatively, he received intravenous ampicillin/ sulbactam (3 g, every 6 hours) for

3 days and was discharged home on no antimicrobial therapy.

Two days after discharge, he was readmitted to the hospital because ascitic fluid was draining through his cholecystectomy ports and the microbiology laboratory reported that a bile culture obtained intraoperatively was growing *L. monocytogenes*. Blood cultures that were negative during the first admission were repeated and were negative once again. Signs and symptoms of CNS infection were absent and a decision was made to refrain from performing a lumbar puncture. The patient was given ampicillin, 2 g every 6 hours intravenously for 5 days and then declined additional intravenous therapy. He was then discharged on oral therapy for 4 more weeks. During the antibiotic treatment period, his TNFIT was withheld. The patient was seen in follow-up 1 month after stopping the antibiotic and had returned to his baseline status.

Discussion

Listeria monocytogenes, a facultative anaerobic grampositive rod, has been receiving more attention lately because of its role in recent outbreaks of food-borne illnesses. *Listeria monocytogenes* infection initiates with a gastroenteritis that often goes undiagnosed. The organism may be controlled at the latter stage or may go

on to disseminate. In patients with impaired cellular immunity, and especially those patients receiving TNFIT, *Listeria* infections have been reported with increasing frequency and have been shown in many individuals to cause significant morbidity and mortality.⁴ Allerberger et al² found that 2 of 467 *L. monocytogenes* isolates were obtained from the gallbladder. Table 1 lists the clinical characteristics of our case and another 5 cases of *L. monocytogenes* cholecystitis reported in the literature. Three patients had rheumatoid arthritis as an underlying condition requiring TNFIT and 2 of those received infliximab. All patients underwent a cholecystectomy combined with antibiotic treatment. Four of the 6 patients received ampicillin or penicillin. Bile cultures grew the organism in 5 of the 6 patients. Pathology reports revealed inflammation of the gallbladder compatible with cholecystitis in 4 patients and were not reported in 2 others. Four of these 6 patients had prolonged and complicated hospital courses; 1 patient died.

Since its introduction in 1998, infliximab, the first tumor necrosis factor (TNF) inhibitor, has been used to treat a number of autoimmune diseases. Tolerability and therapeutic efficacy of both infliximab and etanercept are good, and the number of patients receiving these agents is increasing steadily.⁵ It is well known that TNFIT increases one's susceptibility

to a wide variety of opportunistic pathogens including mycobacteria, fungi and several viruses and bacteria. The latter pathogens require an intact T-helper cell response for recovery.⁶ Among the reported bacterial pathogens, *Listeria* species have been recognized with increasing frequency. The U.S. Food and Drug Administration reported 26 cases of serious *L. monocytogenes* infections in the literature, including 7 deaths, among patients treated with a TNF inhibitor.⁴ A systematic review and meta-analysis also confirmed that TNFiT increased the risk for serious infection.⁷ Our case and 2 previous case reports confirmed the risk for *Listeria* infection associated with TNFiT in patients with rheumatoid arthritis and, in particular, the risk of this pathogen as a causative organism in biliary tract disease.

Begley et al⁸ postulated that *Listeria* may be responsible for enhanced biofilm formation in bile, which may contribute to the survival of this pathogen in the biliary tree. Bile tends to be resistant to bacterial growth. Eimerman⁹ characterized the growth of *Listeria* in bile and the murine gallbladder. *Listeria* apparently possesses resistance genes that allow it to overcome bile's inherent bacterial toxicity. Given its tropism for the gallbladder, it is perhaps surprising that *Listeria* biliary infections are not observed more frequently. Nevertheless, the precise pathogenesis of *Listeria* cholecystitis is unknown.

Although, the Gram's stain of the gallbladder wall in our patient did not reveal gram-positive bacilli, the histological examination revealed inflammation of the gallbladder compatible with cholecystitis. In addition, the bile Gram's stain showed gram-positive bacilli and the cultures grew *L. monocytogenes* suggesting its pathological role. Previously, there have been case reports of *Listeria* infection that include septic arthritis, meningitis and sepsis associated with etanercept; this is the first confirmed case of cholecystitis.^{10,11} Bacteremia and evidence of CNS infection were not observed in our patient. It is possible that the prompt institution of ampicillin/sulbactam may have prevented these serious sequelae.

It is not proven that antibiotics are required for uncomplicated cholecystitis. Nevertheless, most patients who are hospitalized with this diagnosis do receive antibiotic therapy. Guidelines for the empiric selection of antimicrobial agents for biliary tract infections in a variety of clinical settings have recently been published. Agents such as cefazolin, ceftriaxone, cefepime, ciprofloxacin, levofloxacin and vancomycin either alone or in combination with metronidazole have been recommended.¹² Troxler et al¹³ tested 71 strains of *Listeria* species and found that the organism was resistant to the agents listed previously with the exception of cefazolin and vancomycin. Importantly, *Listeria* CNS

infection has been reported to develop during therapy with such agents as first-generation cephalosporins and vancomycin that have in vitro activity but do not cross the blood-brain barrier.^{14,15}

Ampicillin and penicillin with or without aminoglycosides are generally considered the preferred agent for *Listeria* infection. The addition of an aminoglycoside is recommended in serious infection because the penicillins alone are not bactericidal against this organism. An aminoglycoside was not administered to our patient due to the lack of evidence for systemic infection. Trimethoprim-sulfamethoxazole, a bactericidal agent, is thought to be the best alternative for those intolerant to penicillins.¹⁶

The U.S. Food and Drug Administration recently added potentially fatal *Listeria* infection to the list of opportunistic infections that occur in patients who receive TNFi.⁴ We believe that in suspected biliary tract infection in a patient who is being treated with TNFi, strong consideration should be given to an antimicrobial agent that is able to cross the blood-brain barrier and has activity against *Listeria*.

In summary, a patient who manifests signs and/or symptoms suggestive of infection during TNFi must receive a rapid and careful evaluation, with a high

suspicion for unusual pathogens and in particular *L* monocytogenes. In addition, TNFIT likely increases the risk for *Listeria* cholecystitis. Physicians should consider *L* monocytogenes as a cause of cholecystitis in patients who are receiving TNFIT to initiate appropriate treatment and hopefully reduce the potentially severe morbidity and mortality associated with this pathogen.

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TABLE 1. Characteristics of 6 patients with *Listeria monocytogenes* cholecystitis published in the literature, including the case reported in this article

Case	Reference	Age (yr)/sex	Medical history	Diagnosis	Isolation of <i>L. monocytogenes</i>	Biological agent use/anti-TNF product	Treatment	Outcome	Duration of hospitalization/complications
1	Gordon and Singer ¹	76/F	DM, HTN, myocardial infarction	Acute necrotizing cholecystitis	Bile fluid	No	Ampicillin, metronidazole, gentamicin	Recovered	7 d
2	Allerberger et al ²	57/M	NR	Chronic cholecystitis	Bile fluid	No	Doxycycline → mezlocillin → amoxicillin	Recovered	21 d/delayed wound healing
3	Allerberger et al ²	77/F	Bleeding gastric ulcer	Acute cholecystitis	Bile fluid	No	NR	Recovered	12 d
4	Glück et al ³	60/F	Rheumatoid arthritis	NR	Swab culture from the gallbladder, blood	Yes/infliximab	Ceftriaxone, metronidazole, fluconazole	Death	Severe brain edema with subarachnoid hemorrhage
5	Glück et al ³	62/F	Rheumatoid arthritis	NR	Blood	Yes/infliximab	Ampicillin IV, gentamicin	Recovered	18 mo/cerebral abscess
6	This study	56/M	Rheumatoid arthritis, alcoholic cirrhosis	Chronic cholecystitis	Bile fluid	Yes/etanercept	Ampicillin IV → amoxicillin-clavulanate PO	Recovered	3 d (first admission) 4 d (second admission)

DM, diabetes mellitus; F, female; HTN, hypertension; IV, intravenous; M, male; NR, not reported; PO, per oral; TNF, tumor necrosis factor.