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Edwardsiella tarda: A Classic Presentation of a Rare Fatal Infection, with Possible New Background Risk Factors

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Data Interpretation D
Manuscript Preparation E
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Patient: Female, 59-year-old
Final Diagnosis: Sepsis
Symptoms: Acute kidney injury • pancytopenia • respiratory deterioration • sepsis
Medication: —
Clinical Procedure: Mechanical ventilation
Specialty: Critical Care Medicine • Infectious Diseases

Objective: Rare disease

Background: *Edwardsiella tarda* is a facultative anaerobic bacterium that is rarely pathogenic to humans, but, in patients with certain risk factors, it can lead to severe, disseminated infections. Humans are inoculated through the gastrointestinal tract while consuming undercooked or raw seafood or through skin penetration. *E. tarda* has been isolated from marine environments, including lakes, rivers, wells, and sewage water. Although the bacterium has not been directly isolated from seawater, it has been cultured from animals inhabiting seawater environments. In the United States, *E. tarda* is predominantly localized along the coastline of the Gulf of Mexico. Complications from this bacterium usually arise in patients with liver disease, iron overload, or cirrhosis or in those who are immunocompromised or on immunosuppressive therapy.

Case Report: Our patient was a 59-year-old woman with a history of advanced lung cancer, pulmonary hypertension, liver cirrhosis, hepatitis C, and alcoholism. She initially presented to the Emergency Department in the Florida Panhandle on June 16 with colitis, which then progressed to fulminant sepsis with septic shock. Despite aggressive interventions, including intravenous hydration, broad-spectrum antibiotics, and vasopressor support, our patient succumbed to her illness approximately 34 h after initial presentation.

Conclusions: Although severe cases of *E. tarda* have been reported in patients with liver dysfunction, we believe this is the first reported case potentially complicated by concomitant lung cancer.
The rise in sea water temperature, increased human consumption of raw seafood, and increased prevalence of nonalcoholic steatohepatitis may increase the incidence and mortality of *E. tarda* in the near future.

Keywords: *Edwardsiella tarda* • Hepatitis C, Chronic • Vibrio Infections • Global Warming • Cirrhosis, Cryptogenic

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Background

Edwardsiella tarda is an anaerobic facultative gram-negative bacillus belonging to the Enterobacteriaceae family [1]. It is mainly found in ponds and warm and brackish waters along the coastlines of tropical and sub-tropical regions [2,3]. Its carriers include various marine animals and amphibians, such as oysters, fish, seals, lizards, and snakes. The majority of cases involving *E. tarda* infections originate in Japan, China, and the Gulf of Mexico in the United States. It is an unusual pathogen in humans. The Florida Department of Health reports a steady yearly increase in new cases and deaths due to warm water-borne pathogens [4]. Most commonly, patients with *E. tarda* present with gastroenteritis after ingestion of contaminated raw seafood [3]. Rare but severe cases of cellulitis or skin and muscle necrosis as well as osteomyelitis, meningitis, or life-threatening systemic infections after exposure of a wound or laceration to water have been reported [1]. Patients who develop septicemia are usually immunocompromised and have underlying cirrhosis, chronic alcohol abuse, or iron overload [3], resulting in a high mortality rate, even when the treatment is appropriate. The antibiotic regimen for *E. tarda* infections includes standard gram-negative coverage with beta-lactams, third- and fourth-generation cephalosporins, fluoroquinolones, carbapenems, and aminoglycosides, depending on the level of susceptibility [5]. We present the case of a patient with lung cancer, not on chemotherapy, yet she had cirrhosis of the liver and developed fatal *E. tarda* bacteremia after consuming raw oysters. Lung cancer is a potential new comorbidity that can increase the risk of developing a severe infection in this population. Lung cancer has not been reported as a risk factor for *E. tarda*. This is the first reported case of *E. tarda* in a patient with lung cancer.

Case Report

A 59-year-old woman with a history of advanced lung cancer, pulmonary hypertension, cirrhosis of the liver, hepatitis C positivity, and history of alcohol abuse was brought in by ambulance to the Emergency Department of a hospital in the Florida Panhandle, during mid-summer, on June 16, 2021. She had consumed raw oysters the previous day and complained of generalized lower abdominal pain that started the following morning. On initial presentation, the patient complained of a non-radiating dull abdominal ache. She denied fever and chills; there was no associated nausea or vomiting. The patient's vital signs were as follows: blood pressure 75/50 mm Hg; pulse rate, 100 beats/min; and respiratory rate, 22 breaths/min. The patient was afebrile with a temperature of 36.7°C, with no signs of distress, and was nontoxic. Upon physical examination, she did not appear toxic, her lungs were clear, and there was lower abdominal tenderness without peritoneal signs. The following laboratory data were noted: while blood cell (WBC) count, 0.7 K/uL (reference range: 3.8-10.8 K/uL); hemoglobin level, 12.5 g/dL (reference range: 13.5-17.5 g/dL); platelet count, 32 K/uL (reference range: 140-400 K/uL); sodium, 144 mEq/L (reference range: 135-145 mEq/L); potassium, 3.6 mEq/L (reference range: 3.6-5.2 mEq/L); creatinine, 1.75 mg/dL (reference range: 0.59-1.04 mg/dL); BUN, 16 mg/dL (reference range: 6-24 mg/dL); glucose, 71 mg/dL (reference range: 70-100 mg/dL); and albumin, 1.9 g/L (reference range: 3.5-5.5 g/dL).

The urinalysis was positive for infection and was notable for the following: +1 protein, +1 blood, +4 urobilinogen, 2.5 hyaline casts per high power field, 51 to 100 WBCs with clumps.

Her initial computerized tomography (CT) scan of the abdomen and pelvis without intravenous (i.v.) contrast revealed wall thickening throughout the right colon and inflammation extending along the colon and surrounding the terminal ileum and appendix. Portal venous congestion was observed. Cirrhosis of the liver was also confirmed, and there was pulmonary right lower lobe infiltrate, which was also present on the chest radiograph. No splenomegaly was noted on the CT scan. She was admitted to the Intensive Care Unit with a diagnosis of sepsis with shock related to colitis, right lower lobe pneumonia, and urinary tract infection.

Treatment began with i.v. fluid boluses, but after 4 L, she remained hypotensive, and a cardiovascular pressor with norepinephrine broad-spectrum antibiotics was also simultaneously initiated after appropriate blood and urine cultures were collected. Cefepime, metronidazole, and levofloxacin were started to cover the respiratory and intra-abdominal sources of infection. Pharmacologic deep-vein thrombosis prophylaxis was not administered because of the patient's severe thrombocytopenia.

Granix (tbo-filgrastim) was administered. Despite her lung cancer diagnosis, she was not currently receiving chemotherapy but underwent radiation 2 months prior. Initially, her dyspnea was treated with albuterol/ipratropium nebulization every 4 to 6 h, and her oxygen saturation remained above 93%.

The following day, the patient's condition continued to deteriorate. She developed acute hypoxic respiratory failure and progressive encephalopathy, requiring endotracheal intubation and initiation of mechanical ventilation. After endotracheal intubation, an orogastric tube was placed. Septic shock and hypotension persisted, and the patient was also administered albumin and started on continuous sodium bicarbonate infusion of 1 L of D5W with 150 mEq of sodium bicarbonate. Additionally, the vitamin C sepsis protocol was initiated, which included vitamin C, 500 mg i.v. every 8 h, hydrocortisone 100 mg i.v. every 6 h, and thiamine 200 mg i.v. every 8 h [6]. The preliminary blood culture showed gram-negative

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bacteremia, so doxycycline was added for presumptive *Vibrio vulnificus* coverage, considering that she ingested raw oysters. In this part of Florida, we are familiar with *V. vulnificus* infections in the summer as a result of consumption of raw oysters.

The following morning, about 34 h after initial arrival to the Emergency Department, the patient died, despite receiving aggressive treatment with broad-spectrum antibiotics, vitamin C protocol, albumin, i.v. fluid resuscitation, and maxed out cardiovascular pressor support. Prior to the patient's death, the nursing staff reported blisters and boils forming on the patient's upper and lower extremities. The presence of *E. tarda* was revealed in 1 of 2 aerobic and 1 of 2 anaerobic postmortem blood cultures. After positive blood culture was obtained, the blood was plated on a negative combo panel and the results were read with a Beckman Coulter micro scan.

Discussion

Only *E. tarda*, from the genus *Edwardsiella*, is a foodborne and waterborne pathogen that infects humans in 3 different ways. The most common is intestinal presentation, such as gastroenteritis, when raw seafood is consumed. The extraintestinal manifestations can be localized in the form of cellulitis, myonecrosis, or even gas gangrene. This occurs with open wounds, trauma, and loss of skin integrity. These lesions can require surgical intervention. The most serious presentation is a systemic manifestation complex that can include septic shock, osteomyelitis, cholecystitis, and meningitis. Systemic manifestations carry a high risk of mortality [12]. Cirrhosis of the liver, immunocompromised state, and liver disease with iron overload have been the only risk factors reported for severe sepsis with *E. tarda* in humans. Our patient had pancytopenia. It was unclear whether this was a result of hypersplenism from her cirrhosis or was related to sepsis, as her CT scan failed to demonstrate splenomegaly.

E. tarda is a rare human pathogen, but it is a virulent pathogen for fish that causes extensive economic losses in the aquaculture industry worldwide.

As a result, the aqua farm industry is currently working toward producing a vaccine against *E. tarda* for marine life. Recent studies have shown promising results in flounder species utilizing immunogenic anti-recombinant outer membrane protein C and anti-*E. tarda* antibodies generated from the bacterium to yield immunity with an 85% survival rate after inoculation [13].

Another relevant vaccine is *Vibrio*, specifically the Vibrio cholera vaccine. A single-dose, live oral vaccine has been approved by the FDA for the prevention of *V. cholera* in humans. Since *V. cholera* and *E. tarda* have similar bacterial structures, the existing *V. cholera* vaccine may provide the groundwork for future *E. tarda* vaccine development for use in humans.

Data recovered from the Florida Department of Health show that cases of another similar microbe, *V. vulnificus*, increased proportionally with increasing water temperature. In 2008, there were 18 cases, and in 2018, there were 42 reported cases of *V. vulnificus* in Florida alone [14]. Additionally, global sea surface temperature obtained from the Environmental Protection Agency revealed a sustained increase at an average rate of -10°C per decade [15]. Since there is currently no vaccine for humans, and water temperatures in the Gulf of Mexico continue to rise, it is reasonable to believe that *E. tarda* and *V. vulnificus* infections will correspondingly increase. Hence, the need for an *E. tarda* vaccine for humans is warranted. Recent advancements in mRNA vaccine technology amid the SARS-CoV-2 pandemic have removed several barriers in vaccine development, making this possible. Data need to be collected prospectively regarding the prevalence of *E. tarda* infection to better answer this question. Considering the small number of cases of *E. tarda* infections per year, it is not financially practical to develop a vaccine. Instead, employing clean eating practices is an effective measure to avoid contracting both *V. vulnificus* and *E. tarda*.

Certain liver pathologies resulting in cryptogenic cirrhosis may increase the risk of developing a disseminated *E. tarda* infection, including but not limited to nonalcoholic steatohepatitis (NASH) and hepatitis C virus (HCV). According to the Centers for Disease Control, obesity rates have increased significantly from 30.5% to 42.4% from 1999/2000 to 2017/2018, respectively [16]. With the rate of obesity on the rise, data show a corresponding increase in the prevalence of NASH [17]. Owing to recent advancements in novel antiviral therapies, HCV infections have been declining in recent years [16]. It is unclear whether the increase in NASH is correlated with the frequency of *E. tarda* cases. However, it is clear that having cryptogenic cirrhosis increases the risk of developing serious complications, such as septic shock and death, from an *E. tarda* infection. Another risk factor in the development of disseminated *E. tarda* infection is hemochromatosis and iron overload. Current research shows that *E. tarda* growth is stimulated by iron-rich environments. Most strains of *E. tarda* produce and release an exotoxin known as hemolysin. Hemolysin is capable of lysing red blood cells and breaking down the liberated hemoglobin. *E. tarda* releases hemolysin extracellularly in iron-depleted environments, suggesting that iron plays a role in the growth of *E. tarda* [18]. This also demonstrates the catalytic effect of iron on *E. tarda* proliferation.

However, an increase in *E. tarda* infection may parallel the rise of *V. vulnificus* infections. *V. vulnificus* is rare enough to record the number of infections by health authorities only in

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2008 [9,14]. *V. vulnificus* infections in Florida vary yearly and show no correlation with variations in the surface temperature in the Gulf of Mexico. In general, marine pathogens are on the rise in ocean environments [10]. Data on *V. vulnificus* cases are limited.

Conclusions

E. tarda remains a rare human pathogen, with the most common presentation being gastrointestinal presentation. Extraintestinal manifestations have a serious prognosis and are frequently fatal. Thus far, cirrhosis of the liver and iron overload remain the only risk factors for systemic infections. Interestingly, global warming, resulting in increased gulf water temperature, and the increased frequency of liver cirrhosis from NASH, resulting from rising rates of obesity, may explain the increase in reported incidence. Additionally, our patient had a unique risk factor that has not been previously reported, advanced lung cancer, and it is not clear if lung cancer is an independent risk factor. The rise in sea water temperature, increased human consumption of raw seafood, and increased prevalence of NASH may give rise to an increase in the incidence and mortality of *E. tarda* in the near future.

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