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Lactobacillus fermentum, a pathogen in documented cholecystitis

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ABSTRACT

INTRODUCTION: Lactobacillus species are probiotics proven to exhibit various preventative as well as therapeutic properties. While lactobacillus species have been implicated in the formation of dental caries, endocarditis and bacteremia, their role as pathogens in cholecystitis has not been reported. We present a rare case of *Lactobacillus fermentum* working as a pathogen in cholecystitis.
PRESENTATION OF CASE: An 81-year old male was admitted with right upper quadrant abdominal pain. His signs, symptoms, laboratory values and imaging were consistent with a diagnosis of cholecystitis with ascending cholangitis. In view of his co-morbidity and severe sepsis, the patient was treated non-operatively with antibiotics and cholecystostomy. *L. fermentum*, which was vancomycin resistant, was identified from the cholecystostomy aspirate and from anaerobic blood culture. The patient went into septic shock, developed multi-organ dysfunction syndrome and eventually died.
DISCUSSION: Commensal bacteria such as *L. fermentum* are known to modulate immunity, reduce the pathogenicity of gastrointestinal organisms and play a therapeutic role in various disease processes. We isolated *L. fermentum* as a pathogen in a documented case of cholecystitis with ascending cholangitis.
CONCLUSION: While the routine use lactobacillus species as a probiotic is supported in the literature, understanding its potential role as a pathogen may allow more judicious use of these bacteria and encourage research to elucidate the pathogenicity of lactobacillus species.

1. Introduction

Within the past few decades, research has shed light on the complex relationship between the normal flora of the human body and the changes that occur with the use of antibiotics.[1,2] The alteration of this complex balance between the normal flora and ingested microbes has explained the pathophysiology of disease entities such as clostridial infection in the colon.[3] Commensal bacteria such as the lactobacillus species have been shown to play an integral role in preventing colonization by potential pathogens in the colon and are thus designated probiotics.[1,4,5] Oral administration of probiotics has been shown to enhance innate immunity, as well as having antimicrobial and antioxidative activity.[6,7] Probiotics have also been shown to be beneficial in a wide range of disease processes, from urinary tract infection to bacterial vaginosis.[8] On the other hand, lactobacillus species have been reported to act as pathogens in dental caries, endocarditis and bacteremia. However, review of the literature does not reveal any episode of this probiotic acting as a pathogen in cholecystitis.[9–11,13,14] We report an 81-year male who was diagnosed with cholecystitis and ascending cholangitis, from whom *Lactobacillus fermentum* was isolated as the likely pathogen.

2. Case report

An 81-year old male with a past medical history of diabetes mellitus, coronary artery disease, hypertension and dyslipidemia, presented with right upper quadrant abdominal pain. The pain started two weeks prior to admission, during a recent visit to the South America. His initial symptom was vague upper abdominal discomfort, which progressed. One week prior to admission the pain became constant, sharp, severe, non-radiating and localized to the right upper quadrant. It was associated with nausea and non-bilious vomiting. He reported feeling hot but not shivery. While eating worsened the pain, nothing made it better. He reported increasing distension of his abdomen. He had a normal bowel movement two days prior to admission, a normal interval for him. He also had dysuria and persistent hypertension that was previously well controlled.

On physical examination the patient's vital signs were within normal limits. He was an obese, elderly, black male in no acute distress. He had scleral icterus and the base of his tongue was yellow. His obese abdomen was distended with no visible surgical scars; it was dull to percussion and soft to palpation with upper abdominal tenderness, maximal in the right upper quadrant. He had a positive Murphy's sign. He had no other significant physical signs.

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His blood tests revealed a leukocytosis with a white blood count of 13.1 K/μL, (normal 4–10.3 K/μL), anemia with hemoglobin of 8.2 g/dL (normal 12.5–16.9 mg/dL), a mildly elevated international normalized ration of 1.7 and acute renal failure with a creatinine of 3.70 mg/dL (normal 0.67–1.17). His liver function tests were abnormal with direct and total bilirubin of 4.4 mg/dL (normal 0–0.2 mg/dL), and 4.9 mg/dL (normal 0.2–1.0 mg/dL), respectively. His alkaline phosphatase was 526 u/L (normal 50–136 u/L). A right upper quadrant ultrasound demonstrated cholelithiasis, gall bladder wall thickening and peri-cholecystic fluid. The common bile duct (CBD) was normal in caliber and did not contain any stones. His urine culture was positive for candida.

The patient's history, physical findings, biochemical values and imaging appeared consistent with cholecystitis and ascending cholangitis. However, given his multiple co-morbid conditions, prolonged history of abdominal pain and presenting sepsis, a decision was made to manage the patient non-operatively. The antibiotics, aztreonam and metronidazole for gram negative and anaerobic coverage respectively, were started. He was admitted to the surgical intensive care unit. Micafungin was added for the candiduria and the probiotic *Lactobacillus acidophilus* was also started on the day of admission. On hospital day 1, magnetic resonance cholangio-pancreatography demonstrated a normal CBD, intra-hepatic and extra-hepatic ducts. Endoscopic ultrasound was negative for any CBD pathology.

The patient initially responded to the aforementioned therapy; his leukocytosis improved, he was afebrile and his mentation improved. However, his condition began to deteriorate by hospital day 8. He had a progressive increase in total bilirubin, which peaked at 20 mg/dL, and increased coagulopathy. On hospital day 9 he became hypoxic with depressed mental status, requiring endotracheal intubation. An abdominal computed tomography (CT) scan demonstrated pericholecystic inflammatory changes and fluid, suggestive of gallbladder perforation with possible hepatic abscess. A CT guided cholecystostomy was performed that same day. 150 ml of dark brown fluid was aspirated. Cultures from the cholecystostomy aspirate grew *L. fermentum*, resistant to vancomycin. Blood cultures sent the same day came back with the same microbiology, whereas the blood cultures drawn on admission did not have any bacterial growth. Subsequently the antibiotics were switched to linezolid, to which the organism was sensitive. The patient remained on linezolid throughout his hospitalization. The lactobacillus probiotic was discontinued at that time. The patient continued to deteriorate.

On hospital day 13, a repeat CT of the abdomen demonstrated regression of the gallbladder and hepatic collection, but ascites was seen. CT guided drainage was performed of the fluid: it was clear and straw colored and there was no growth on culture. Repeat CT of the abdomen on hospital day 20 showed complete resolution of the liver abscess and ascitic fluid. Although the initial source of infection appeared controlled, the patient's candiduria persisted, and he developed pneumonia. Micafungin had been switched to fluconazole on hospital day 10, and the antibiotic coverage was broadened to include piperacillin/tazobactam (Zosyn) to cover the pneumonia, the sensitivity determined on culture of broncheo-alveolar lavage. Linezolid was continued. Despite these measures, he developed overwhelming sepsis, requiring norepinephrine and vasopressin drips. On hospital day 25, he became agitated, bit on his endotracheal tube, had a cardiac arrest and was successfully resuscitated, but died on hospital day 26.

3. Discussion

The beneficial interaction between probiotics and the endogenous flora in the gastrointestinal tract is clear.[11,12,15] Hence for the foreseeable future, probiotic administration, particularly when antibiotics are being used, would seem to be acceptable practice.[16] However, there have been many reports in the literature implicating lactobacillus as the pathogen for various infections, particularly, bacteremia and endocarditis, with the lactobacillus species casei and rhamnosus being the commonest culprits.[13–15] Previous reports suggested that the incidence of infections caused by lactobacilli species is very low (0.08–0.2%)[14–16] and such infection on its own is rarely fatal.[13] However co-infection with lactobacillus species can be a marker of severe infection and risk factor for prolonged hospitalization, or even death.[15,16] A retrospective review of 200 cases,[16] quoted an overall mortality of 30% with a greater mortality associated with polymicrobial infection.[16] Since Lactobacilli are part of the normal flora of the gastrointestinal and genitourinary tracts,[13] it can be difficult to determine when an infection is caused by an endogenous species or one that is administered. There is a theoretical risk of potential transmigration of probiotics in the gastrointestinal tracts leading to colonization or even infection, through the alteration of normal physiology.[17] However, the literature has not demonstrated a link between administered probiotics and subsequent infections.[14] Our patient received *L. acidophilus* early in his admission, a different species from the *L. fermentum* that we isolated. Therefore, it is likely that the pathogen was endogenous within his gastrointestinal tract. Nevertheless, we discontinued the probiotic once the culture was finalized.

We believe that the lactobacillus species isolated in our patient was serving as a pathogen as opposed to mere colonization, especially as this particular antibiotic-resistant strain of lactobacillus was isolated from two normally sterile sites. Although the pathogen was not cultured until day 9, we believe it to be the source of the patient's initial symptoms rather than an opportunistic or superseding infection. While lactobacillus is usually isolated as part of a polymicrobial infection, our patient did not have any other bacteria grown on culture. This supports the argument that the bacterium served as a primary pathogen. On presentation, the patient received antibiotics for gram-negative coverage; whilst this practice suffices for most cases of cholecystitis[18] it was not adequate for the *L. fermentum* in our patient. The natural history prevailed and he deteriorated. This would explain why his initial blood culture was negative. The blood culture sent on hospital day 9 was positive for *L. fermentum*, the same strain identified from the cholecystostomy aspirate. When placed on appropriate antibiotics, the patient's clinical condition initially improved but concomitant infections (of the urinary tract, and pneumonia) contributed to his demise.

The literature suggests that early cholecystectomy (within 48–72 h of the onset of symptoms) can lead to a better outcome in acute cholecystitis.[19,20] But, there is also evidence that elderly patients with multiple co-morbid conditions do better with non-operative management of acute cholecystitis.[21] Our patient presented two weeks after the onset of his symptoms, with clinical evidence of sepsis. Operative management was therefore not deemed a wise choice especially as he had improved initially on appropriate antibiotics, with adequate percutaneous drainage. His clinical course suggests that the development of pneumonia and unresolved candiduria, in addition to his overwhelming systemic response, played a greater role to his demise than the cholecystitis. This assessment is supported by the literature on lactobacillus infections, which usually serve as a nidus for other infections.[16]

4. Conclusion

To our knowledge, this is the first report of a lactobacillus species being implicated in cholecystitis. Although this report would not justify discontinuing all use of lactobacillus species as a probiotic, it does however highlight a potential risk from the liberal use of

bacteria with pathogenic potential and may stimulate research into how this species can transform to a pathogen.

Conflict of interest statement

None.

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None.

Ethical approval

Written consent was obtained and can be provided upon request by the editor.

Author contributions

Josue Chery, MD – Study design, writing. Dmitriy Dvoskin, MD – Literature search. Fernando P. Morato, MD, FACP – Data collections, editing. Bashar Fahoum, MD, FACS – Study design and writing.

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