1. Introduction

The human intestinal lumen contains millions of living organisms that help in absorption of nutrients and production of organic compounds including vitamin K. Lactobacillus is an anaerobic, acid-producing, gram-positive rod, widely known as a group of probiotic bacteria. It is generally regarded as one of the ‘good’ bacteria. They are part of the normal flora of the oral cavity, GI, and the female GU tract. There are many species of lactobacilli identified, four of which are clinically used as probiotics; *L. acidophilus*, *L. bulgaricus*, *L. reuteri*, and *L. rhamnosus* GG. Amongst these species, *L. acidophilus* is the dominant bowel bacteria. Generally, lactobacillus preparations are used to maintain and restore the normal intestinal bacterial flora. They do so by producing lactic acid and hence creating an acidic environment unfavorable for the growth of other pathogens such as bacteria and fungi. They also produce lactases, lipases, and proteases that may aid in digestion. Because of their role as probiotics, lactobacillus preparations have been used, and have shown efficacy, in treatment and prevention of antibiotic-associated diarrhea, acute gastroenteritis in children, atopic dermatitis in infants, constipation, inflammatory bowel disease, and nonalcoholic fatty liver disease[1].

Lactobacillus, despite their many beneficial roles in humans, do have the potential to translocate out of their normal environment and cause serious illness in the right patient and under the appropriate circumstances. Lactobacillus bacteremia, sepsis, and endocarditis have been reported in a number of cases in the past [2,3]. These severe infections have occurred in patients with underlying diseases such as uncontrolled diabetes mellitus, valvular heart disease, immunocompromised (HIV, chronic steroids, chemotherapy), short bowel syndrome, and hematologic malignancies [4–6]. Some associated risk factors include dental procedures, use of total parenteral nutrition, IV drug abuse, abdominal surgery, and excessive dairy product consumption or probiotic use [7–9].

Although rare, Lactobacillus liver abscess has been reported in a total of 9 case reports in the literature [9–17]. Review of literature was done using keywords ‘lactobacillus’ ‘liver abscess’ ‘bacteremia’, through PubMed and MeSH databases with no restrictions for date range. In each of those cases, there were many of the aforementioned risk factors above and comorbidities associated with the presentation of lactobacillus bacteremia and liver abscess. We present a case of lactobacillus bacteremia and liver abscess in a 46-year-old male with past medical history significant for newly diagnosed uncontrolled diabetes mellitus in the US, this case underscores the need to consider ‘good’ Lactobacillus as a potential pathogen in this patient population.

2. Case presentation

We present a case of a 46-year-old Hispanic male with a past medical history of newly diagnosed uncontrolled diabetes (hemoglobin A1c 9.9%) who comes in with a three-week history of worsening generalized abdominal pain and body aches associated with persistent fevers, nausea, and vomiting. In addition, he has had a decreased appetite for the last three weeks as well as an unintentional 50-pound weight loss over the last two years. He is originally from Mexico; however, he had not traveled out of the US for 10 years. He lives alone and...
works as a carpenter. He denies any use of tobacco, alcohol, sexually transmitted diseases, or illicit drug use.

On admission, vitals were as follows: temperature 38.6°C (101.5°F), heart rate 103, respiratory rate 16, 97% oxygen saturation on room air. Physical exam was significant for the presence of a thin looking, malnourished male, BMI 20.7. Cardiovascular exam was significant for tachycardia. Pulmonary examination revealed decreased breath sounds bilaterally and right lower lobe rales. Abdominal examination was positive for a tender abdomen to moderate palpation localized to the epigastrium and right upper-quadrant region. No splenomegaly, and unable to assess hepatomegaly due to significant pain on palpation or percussion.

Laboratory studies revealed the following: complete blood count (CBC) was significant for leukocytosis 16.2x10^3 µL and hemoglobin 11.9 g/dL. Comprehensive metabolic panel (CMP) was significant for sodium 123 mEq/L, chloride 84 mEq/L, albumin 2.9, total bilirubin 2.2 mg/dL (0.8 direct, 1.4 indirect), alkaline phosphatase 349 IU/L, ALT/AST 104/92 IU/L, glucose 304 mg/dL. Lactic acid 2.0 mmol/L.

Due to concern for an intra-abdominal pathology a CT abdomen and pelvis with contrast (Figure 1) and abdominal ultrasound were performed which revealed the following:

Abdominal ultrasound showed evidence of a diffusely heterogeneous liver with multiple areas of hyperechogenicity involving the right and left lobes measuring 12.9 × 16.4 × 11.1 cm. The gallbladder was distended with gallstones and a thickened gallbladder wall.

The patient was admitted to the hospital for further management of a suspected large multiloculated liver abscess. Diagnostic considerations at this time included a pyogenic abscess versus invasive amoebic abscess, and we subsequently started a combination of ampicillin-sulbactam and metronidazole. Stool studies for ova and parasites, Clostridium difficile, Cryptosporidium antigen, fecal leukocytes, stool culture, and Giardia antigen were negative. Serologies for Entamoeba histolytica, Echinococcus, hepatitis, HIV, interferon gamma assay were all unrevealing. Blood cultures revealed the growth of a Lactobacillus species. Exact speciation was never obtained by our hospital lab.

After stabilization, the patient was sent to interventional radiology for CT guided percutaneous abscess aspiration and drainage involving the largest loculation. This resulted in significant drainage output, 80 to 120 mL per day of a thick, milky, purulent fluid. Gram stain and culture from the aspirate also grew Lactobacillus species; however, the exact strain was never identified. MRCP was performed to evaluate for common bile duct dilation and ascending biliary infection, which was unremarkable. Echocardiogram was performed and revealed no valvular vegetations.

Throughout his hospital stay, our patient underwent periodic IR guided catheter drainage and manipulations to drain the adjacent contiguous loculations in the liver. In addition, there was an interval development of a subdiaphragmatic fluid collection, which required placement
of a second drain. Furthermore, a moderate right-sided pleural effusion was also noted. The patient underwent thoracentesis, and the fluid was consistent with an exudative effusion.

Three weeks after the admission, our patient was re-imaged one final time (Figure 2) which showed dramatic resolution of his liver abscess, as well as improvement in the subphrenic fluid collection and right-sided pleural effusion. The second drain that was placed for the subphrenic fluid collection was removed before discharge, and the original drain for the liver abscess was removed one week later. He was discharged home to complete a total of 5 weeks of antibiotics, the last 2 weeks with amoxicillin-clavulanate based on cultures and sensitivities (Appendix; Table 1).

3. Discussion

When evaluating a patient with a liver abscess, the most common etiology is a pyogenic liver abscess accounting for 48% of visceral abscesses and 13% of intra-abdominal abscesses overall [18]. It has similar risk factors to Lactobacillus liver abscess such as diabetes, hepatopancreatobiliary, and intracolonic disease. Important microbiological causes of pyogenic liver abscess include gram-negative bacilli (Escherichia coli, Klebsiella pneumonia) and streptococci [19]. Therefore, when presented with a patient with a liver abscess, a pyogenic liver abscess should be strongly considered and treated empirically covering the most common bacteria.

Cases of Lactobacillus bacteremia and liver abscess are extremely rare in the literature. This makes understanding the pathophysiology and etiologies of this rare infection that much more challenging. The known entities in the literature that predispose patients to this exceedingly rare infection include immunosuppression, uncontrolled diabetes, bacterial translocation, and use of probiotics.

Other case reports (Appendix; Table 2) have identified probiotics as the etiology for the development of Lactobacillus liver abscess [9,17]. The use of probiotics has become widespread over the past few decades. Although their mechanism of action remains incompletely understood, they are thought to improve intestinal function by maintaining the integrity of the epithelial and mucosal layers of the colon. They then enhance the mucous layer and strengthen the tight junctions of the intestinal epithelial mucosa. They are also thought to decrease apoptosis through production of protective cytokines (such as IL-10 and TGF-b) [20].

Our patient did not have a history of extensive probiotic intake or probiotic-rich foods such as yogurt and other dairy products, eliminating this as a factor in our case. The only identified known risk factor for our patient was his diabetes, which combined with lack of health insurance presented as uncontrolled diabetes. Diabetes mellitus is associated with two types of vascular disease. Non-occlusive microangiopathy, which is caused by increased vascular permeability and impaired autoregulation of blood flow involving the capillaries and arterioles. Macroangiopathy is associated with atherosclerotic lesions [21]. In addition, advanced glycation end products (AGEs) are responsible for glycosylation of basement membranes resulting in increased vascular permeability. Metabolic alterations in diabetes have also been reported to contribute in changes in endothelial cells. This is likely a factor in the higher susceptibility of diabetic patients to deadly complications of infectious diseases. This endothelial injury could be a possible route of bacterial translocation from normal flora to bacteremia and formation of liver abscess.

A PubMed and ClinicalKey review of the literature identified six cases (out of eight reported cases of Lactobacillus liver abscess) that occurred in diabetics. However, each of those reported cases had an additional underlying disease process, particularly involving the hepatobiliary system such as post-cholecystectomy, ERCP, cholangitis, and Mirizzi syndrome, or other intestinal pathology including Crohn’s disease [10,12,14,16,17]. Our patient only had uncontrolled diabetes thus predisposing him to increased risk of endothelial injury and bacterial translocation. However, without any evidence of other underlying predisposing factors mentioned above, this is the first case of Lactobacillus liver abscess in which there was no identifiable inciting event.

Studies have shown that certain species such as L. rhamnosus GG is acid and bile stable which could explain the close association between hepatobiliary pathology and lactobacillus liver abscess [22]. With this knowledge, a hepatobiliary source was evaluated with both an MRCP and abdominal ultrasound. MRCP showed no evidence of choledocholithiasis and no common bile duct dilatation. Abdominal ultrasound showed 5 mm common bile duct dilatation, distended gallbladder and thickened gallbladder wall. Particularly, in regards to the abdominal ultrasound, there are radiographic signs of biliary pathology; however, it is unclear whether this was a primary pathology which led to seeding of the liver or secondary to the liver abscess causing the biliary abnormalities. This perhaps could have been better evaluated with repeat abdominal ultrasound and/or MRCP as the liver abscess resolved, however would be unlikely to change overall management.

Lactobacillus bacteremia is typically indicative of profound immunosuppression and carries an overall poor prognosis with associated 30% mortality [23]. Due to this association, our patient was extensively worked up for other immunosuppressive comorbidities including HIV, immunoglobulin deficiencies, steroid use, and workplace exposures, all of which came back negative. Given that our patient was relatively young with previous good functional capacity and did not
experience any complications or require surgical inter-
vention during his hospitalization he was able to make
a full recovery. In addition, upon this outpatient visit
after completion of antibiotic course and removal of his
percutaneous drainage, he remained asymptomatic and
was able to return to work in full capacity, all of which
point to an excellent prognosis going forward.
Furthermore, with improved control of his diabetes,
we expect this is highly unlikely to recur in the future.

Given the increasing prevalence of diabetes mellitus in
the USA and use of probiotics, it is expected that more
cases of Lactobacillus bacteremia and liver abscess would
be reported in the future[24]. In regards to the use of
probiotics, the prevalence is likely underestimated given
the presence of probiotics in other common foods such as
milk, yogurt, and other dairy products[25]. This is in
addition to their application in medicine for increasingly
common conditions such as antibiotic-associated diar-
rhea and inflammatory bowel disease. Furthermore, as
patients are living longer and longer with diabetes and
our ability to manage complications of uncontrolled
diabetes improve the population of individuals at risk
for Lactobacillus bacteremia will continue to increase.
The same can be said for the increasing prevalence of
other associated risk factors such as immunosuppression,
hematological malignancies, and valvular disease.
Therefore, the combination of increasing probiotic use
and increasing population at risk for of Lactobacillus
bacteremia the cases of Lactobacillus liver abscess should
be expected to rise in the future. How quickly it would
rise remains to be seen. It would therefore be of use to
further study Lactobacillus for its virulence factors so that
its pathogenesis may be better understood and its com-
lications better prevented and treated.

Disclosure statement
No potential conflict of interest was reported by the authors.

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Appendix:

Table 1. Lactobacillus culture and sensitivities

| Antimicrobial        | MIC (µg/mL) |
|----------------------|-------------|
| Ampicillin/sulbactam | 0.06        |
| Clindamycin          | 1           |
| Imipenem             | 0.25        |
| Meropenem            | 2           |
| Metronidazole        | >256        |
| Penicillin           | 0.03        |

Table 2. Summary table of Lactobacillus bacteremia and liver abscess case reports:

| Case            | Risk factors                                         | Species     | Treatment                                             | Reference               |
|-----------------|------------------------------------------------------|-------------|-------------------------------------------------------|-------------------------|
| 75-year-old male| Hepatocellular carcinoma status post intratumoral ethanol injection | L. plantarum | Antibiotics                                           | Isobe, 1990             |
| 39-year-old male| Diabetes, chronic pancreatitis, choledochoduodenostomy | L. acidophilus | Antibiotics                                           | Larvol, 1996            |
| 74-year-old female | Hypertension, excessive dairy consumption          | L. rhamnosus | Percutaneous drainage plus antibiotics                 | Rautio, 1999            |
| 73-year-old female | Diabetes                                             | L. rhamnosus | Surgical drainage plus antibiotics                      | Natario, 2003          |
| 27-year-old male | Crohn’s disease, chronic steroids                    | L. acidophilus | Percutaneous drainage plus antibiotics                 | Cukovic-Cavka, 2006    |
| 51-year-old female | None                                                 | L. paracasei | Percutaneous drainage plus antibiotics                 | Burns, 2007             |
| 74-year-old male | Diabetes, Mirizzi syndrome                           | L. rhamnosus | Percutaneous drainage, cholecystectomy plus antibiotics| Chan, 2010              |
| 82-year-old female | Diabetes, cholecystectomy, probiotic use            | Not identified | Percutaneous drainage plus antibiotics                 | Sherid, 2016            |