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Case Report

Lactococcus lactis cholangitis and bacteremia identified by MALDI-TOF mass spectrometry: A case report and review of the literature on *Lactococcus lactis* infection☆

Akihiko Shimizu [a, *], Ryota Hase [a, b], Daisuke Suzuki [a], Akihiro Toguchi [c], Yoshihito Otsuka [c], Nobuto Hirata [d], Naoto Hosokawa [a]

[a] Department of Infectious Diseases, Kameda Medical Center, 929 Higashicho, Kamogawa, Chiba, 2968602, Japan
[b] Department of Infectious Diseases, Japanese Red Cross Narita Hospital, 90-1 Iidacho, Narita, Chiba, 2868523, Japan
[c] Department of Laboratory Medicine, Kameda Medical Center, 929 Higashicho, Kamogawa, Chiba, 2968602, Japan
[d] Department of Gastroenterology, Kameda Medical Center, 929 Higashicho, Kamogawa, Chiba, 2968602, Japan

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ABSTRACT

Lactococcus lactis is a rare causative organism in humans. Cases of *L. lactis* infection have only rarely been reported. However, because it is often difficult to identify by conventional commercially available methods, its incidence may be underestimated. We herein report the case of a 70-year-old man with cholangiocarcinoma who developed *L. lactis* cholangitis and review previously reported cases of *L. lactis* infection. Our case was confirmed by matrix-assisted desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS). This case shows *L. lactis* is a potential causative pathogen of cholangitis and that MALDI-TOF MS can be useful for the rapid and accurate identification of *L. lactis* infection. We searched the literature for published case reports on cholangitis and any other infections caused by *L. lactis*, and thereby identified 36 cases, including our case. At least 66.7% (n = 24) of the cases had significant underlying conditions; 15 of the cases involved patients with an immunocompromised status. At least 41.7% (n = 15) had a significant food consumption history, such as the consumption of unpasteurized dairy products. The clinical sources of *L. lactis* were diverse and endocarditis was the most common diagnosis (n = 8), followed by hepatobiliary infection (n = 6), central nervous system infection (n = 5), and peritonitis (n = 4). The prognosis was favorable in most cases.

1. Introduction

Lactococcus lactis, formerly known as *Streptococcus lactis*, is a facultative anaerobic, Gram-positive coccus [1]. Although *L. lactis* is usually considered to be non-pathogenic in humans, there have been some case reports describing human infections caused by *L. lactis* [2–35]. In addition, the incidence of *L. lactis* may be underestimated because it is often difficult to identify by conventional methods [36]. We herein report a case of cholangitis due to *L. lactis* that was identified by matrix-assisted desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and review the reported cases of *L. lactis* infection.

2. Case report

A 70-year-old Japanese man with a history of hypertension presented with a 3-day history of dark urine. He also complained of heartburn and constipation. Computed tomography and ultrasound showed dilation of the biliary tracts and his serum bilirubin level was elevated. He was diagnosed with distal cholangiocarcinoma with bile duct obstruction based on an endoscopic biopsy of the bile duct. A bilio-duodenal drainage tube was endoscopically placed and his jaundice was alleviated. No metastatic lesions were noted on additional imaging examinations. He was subsequently discharged and surgical resection was planned.

☆ All authors meet the ICMJE authorship criteria.

* Corresponding author.
E-mail address: shimizu.akihiko@gcmc.pref.gunma.jp (A. Shimizu).

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On day 3 after discharge, the patient presented to the emergency department of our hospital complaining of epigastric pain. At the time of the initial assessment, he was hemodynamically stable and his body temperature was 38.2 °C. A physical examination revealed tenderness of the upper abdomen and Murphy's sign was observed. CT showed a dilated intrahepatic biliary tree (Fig. 1); however, the biliary drainage tube was not dislocated (Fig. 2). According to these findings, he was diagnosed with cholangitis due to drainage tube obstruction. A laboratory analysis revealed leukocytosis (14,200/μL) with neutrophilia and elevated transaminase, alkaline phosphatase, gamma-glutamyltransferase, and bilirubin levels. Blood samples were collected for culturing. Endoscopic retrograde cholangiopancreatography (ERCP) was performed. The obstructed biliary drainage tube was removed and white bile was collected from the obstructed common bile duct via an ERCP catheter, then a new bilio-duodenal tube was inserted. Two sets of blood cultures were prepared using BD BACTEC 92F aerobic and 93F anaerobic media (Becton, Dickinson and Company, Franklin, Lakes, NJ, USA). We then initiated treatment with tazobactam/piperacillin (2.25 g every 6 hours) as empiric therapy.

After 13 hours, one of the anaerobic blood cultures turned positive and Gram-positive cocci (GPC) were detected. We added vancomycin (loading dose of 1.25g, then 0.5 g every 12 hours) to treat potentially penicillin-resistant GPC. MALDI-TOF MS (MALDI Biotyper; Bruker Daltonics, Billerica, MA, USA) identified the isolate as *L. lactis* with a high confidence score (2.339). *L. lactis* was also identified from a bile culture. We performed susceptibility testing using the broth microdilution method and interpreted minimum inhibitory concentrations (MICs) based on *Streptococcus* spp. breakpoints according to M45-A3 [37], published by the Clinical and Laboratory Standard Institute (CLSI), because experimental data on the MICs for *Lactococcus* are limited, and the breakpoints of *Lactococcus* spp. are the same as those of *Streptococcus* spp. Strains isolated from blood and bile cultures were susceptible to ampicillin, erythromycin, clindamycin, and vancomycin (Table 1). Clindamycin susceptibility was also confirmed by a D-test [38]. Tazobactam/piperacillin and vancomycin were discontinued and sulbactam/ampicillin 1.5 g every 6 hours was started on day 5 after admission. Soon after endoscopic drainage, his symptoms were relieved and his bilirubin and hepatobiliary enzyme levels decreased. The bacteremia had originated from cholangitis and the clinical course after initiating the treatment was good. Thus, we considered it unlikely that his condition was caused by endocarditis and did not perform echocardiography. After 14 days of antibiotic therapy (tazobactam/piperacillin for 4 days and vancomycin for 3 days, followed by sulbactam/ampicillin for 10 days), the patient underwent pancreatoduodenectomy to resect the primary lesion. At 2 months after surgery, CT revealed multiple liver metastases; he died shortly after their detection.

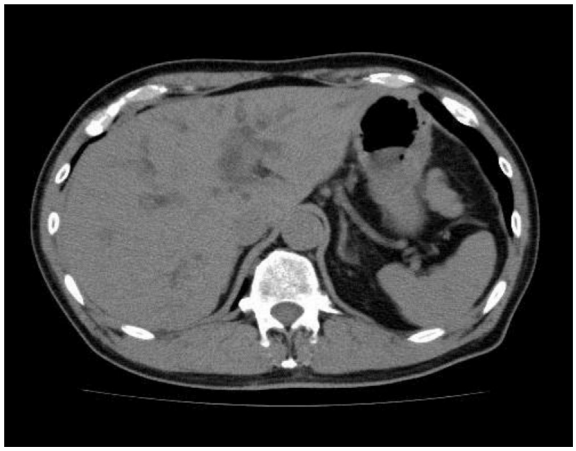

Fig. 1. Abdominal computed tomography revealed a dilated intrahepatic biliary tree.

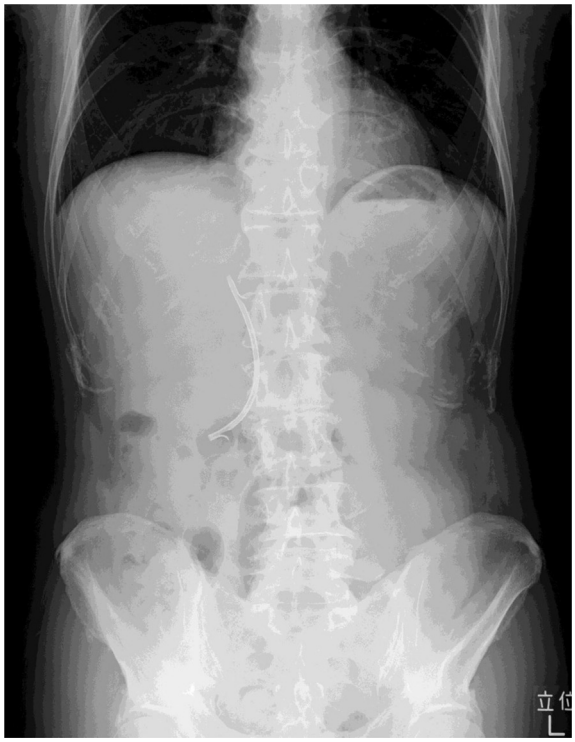

Fig. 2. Abdominal X-ray revealed that the biliary tube was not dislocated.

Table 1
The antibiotic susceptibility of the *Lactococcus lactis* isolated in the present case.

Antibiotics	MIC (μg/mL)	Interpretation
Penicillin	0.25	I
Ampicillin	0.25	S
Erythromycin	0.12	S
Clindamycin	0.25	S
Vancomycin	0.5	S

3. Discussion

To the best of our knowledge, this is only the second report of cholangitis caused by *L. lactis*. The only other case report described *L. lactis*-associated cholangitis in a female patient who developed ascending cholangitis and bacteremia due to an impacted common bile duct stone. The colonization of *L. lactis* in the digestive tract and the occurrence of biliary obstruction are considered to be the two pathogenic factors underlying this rare condition since hepatobiliary tract infections are generally caused by organisms colonizing the human digestive tract. No significant food consumption history was obtained for either cases. However, Maruo et al. [39] showed that *L. lactis* was detected in the feces of three of seven healthy subjects before the administration of the fermented milk containing this species. This indicates that *L. lactis* occasionally colonizes the human gastrointestinal tract. The cholangiocarcinoma in the present case and the common bile duct stone in the previously reported case were thought to have contributed to the onset of cholangitis, since both factors induced biliary obstructions.

Table 2
The reported cases of *Lactococcus lactis* infection.

Diagnosis	Age (years)	Sex	Underlying condition	Known exposure	Identification method	Antimicrobial treatment (duration of therapy)	Outcome	Author (year)	Country	Reference
Endocarditis (n = 8)										
Endocarditis	65	F	Myocardial infarction, rheumatic fever	NA	NA	Benzylpenicillin + gentamicin	Recovered	Mannion (1990)	UK	2
Endocarditis	21	M	Root canal treatment of a molar tooth	Sour cream	Biochemistry	Penicillin + dihydrostreptomycin (22 days)	Recovered	Wood (1995)	USA	3
Endocarditis	56	M	Chronic glomerulonephritis	None	Biochemistry	Penicillin G → clarithromycin (30 days)	Recovered	Pellizzer (1996)	Italy	4
Endocarditis	67	M	None	Unpasteurized milk	Biochemistry	Amoxicillin/clavulanate + gentamicin (15 days) → penicillin (6 weeks)	Recovered	Halldórsdóttir (2002)	Iceland	5
Endocarditis	55	M	Atrial myxoma	None	Biochemistry and 16S rRNA	Amoxicillin/clavulanate (4 weeks)	Recovered	Zechini (2006)	Italy	6
Endocarditis, mycotic aneurysm	49	M	None	Cheese	NA	Penicillin + ceftriaxone + gentamicin (7 weeks)	Recovered	Resch (2008)	Germany	7
Endocarditis	41	M	None	None	Biochemistry	Penicillin G (20 days)	Dead	Lin (2010)	Taiwan	8
Endocarditis	75	M	Mitral valve repair	NA	NA	Vancomycin + gentamicin (8 weeks)	Recovered	Rostagno (2013)	Italy	9
Hepatobiliary infections (n = 6)										
Cholangitis	70	M	Cholangiocarcinoma	None	MALDI-TOF MS	Tazobactam/piperacillin (5 days) + vancomycin (4 days) →sulbactam/ampicillin (9 days)	Recovered	Shimizu (2018)	Japan	Present case
Cholangitis	72	F	None	None	NA	Ciprofloxacin → tazobatam/piperacillin → amoxicillin/clavulanate (2 weeks)	Recovered	Davies (2009)	UK	10
Liver abscess	14	F	None	None	Biochemistry	Cefotiam + amikacin + clindamycin →panipenem/betamipron → piperacillin + amikacin (35 days)	Recovered	Nakarai (2000)	Japan	11
Liver abscess	79	F	None	None	Biochemistry	Imipenem/cilastatin (5 weeks)	Recovered	Antolín (2004)	Spain	12
Liver abscess, portal vein thrombosis	26	M	NA	None	Biochemistry	Meropenem + teicoplanin + metronidazole → meropenem (45 days)	Recovered	Guz (2006)	Turkey	13
Liver abscess, empyema	42	M	None	None	Biochemistry	Ciprofloxacin + metronidazole (4 days) → cefotaxim + metronidazole (18 days) → levofloxacin	Recovered	Kim (2014)	South Korea	14
Central nervous system infections (n = 5)										
Cerebellar abscess	45	F	None	NA	Biochemistry	Ceftriaxone (8 weeks) + gentamicin (2 weeks) + metronidazole	Recovered	Akhaddar (2002)	Morocco	15
Meningitis	0	M	Prematurity	None	Biochemistry	Vancomycin (3 days) + cefotaxime (12 days)	Recovered	Uchida (2011)	Japan	16
Brain abscess	1	F	Otitis media	Unpasteurized milk and yogurt	NA	Ceftriaxone (12 days) + vancomycin (12 days) + metronidazole (6 days) →meropenem + vancomycin (4 weeks)	Recovered	Topçu (2011)	Turkey	17
Cerebellar abscess	8	M	None	None	NA	Vancomycin + ceftriaxone + metronidazole→ ampicillin (23 days) → amoxicillin/clavulanate + cefuroxime (10 weeks)	Recovered	Feierabend (2013)	Germany	18
Subdural empyema	33	M	Dental caries, sinusitis	None	Biochemistry	Meropenem → ampicillin (4 weeks) → clarithromycin (2 weeks)	Recovered	Inoue (2014)	Japan	19
Peritonitis (n = 4)										
Peritonitis	67	M	CAPD	Yoghurt	NA	1st episode Cefazolin + amikacin 2nd episode Vancomycin (14 days)	NA	Mat (2003)	Belgium	20
Peritonitis	63	M	CAPD	Yoghurt	NA	Vancomycin (21 days) + gentamicin (2 days)	Recovered	Lafrance (2006)	Canada	21
Peritonitis	46	F	CAPD, diabetes mellitus	Yoghurt	Biochemistry	Vancomycin (14 days) + ceftazidime (3 days)	NA	Güz (2008)	Turkey	22
Peritonitis	71	M	CAPD, diabetes mellitus	Butter	NA	Cefazolin + ceftazidime (3 days) → vancomycin + ceftazidime (14 days) → ciprofloxacin (7 days)	Recovered	Lee (2014)	South Korea	23

(*continued on next page*)

Table 2 (*continued*)

Diagnosis	Age (years)	Sex	Underlying condition	Known exposure	Identification method	Antimicrobial treatment (duration of therapy)	Outcome	Author (year)	Country	Reference
Bacteremia (n = 3)										
Bacteremia	69	M	CLL	Yoghurt	NA	Cefotaxime + amikacin	NA	Durand (1995)	France	24
Bacteremia	0	M	Malnutrition	None	Biochemistry and 16S rRNA	Vancomycin + cefepime → vancomycin (14 days)	Recovered	Karaaslan (2016)	Turkey	25
Bacteremia	0	F	Malnutrition	None	Biochemistry and 16S rRNA	Vancomycin (10 days)	Recovered	Karaaslan (2016)	Turkey	25
Deep neck infections (n = 3)										
Neck abscess	68	M	Previous malignancy	Unpasteurized milk cow breeder	Biochemistry	Ceftriaxone + metronidazole (6 weeks)	Recovered	Koyuncu (2005)	Turkey	26
Neck abscess	middle-aged	F	Diabetes mellitus	Unpasteurized milk and cheese	NA	Amoxicillin/clavulanate	Recovered	Hadjisymeou (2013)	UK	27
Thyroid abscess	17	F	Anorexia nervosa	None	NA	Amoxicillin (2 weeks)	Recovered	Campos (2015)	Spain	28
Catheter-related bloodstream infection (CRBSI) (n = 2)										
CRBSI	0	F	Prematurity	None	Biochemistry and 16S rRNA	Vancomycin + cefotaxime (14 days)	Recovered	Glikman (2010)	Israel	29
CRBSI	1	M	Down syndrome, Hirschsprung disease	None	Biochemistry	Vancomycin (10 days)	Recovered	Karaaslan (2015)	Turkey	30
Pneumonia (n = 2)										
Necrotizing pneumonia, empyema	24	M	HIV infection	Unpasteurized milk, cheese	Biochemistry	Penicillin + clindamycin (15 days)	Recovered	Torre (1990)	Norway	31
Necrotizing pneumonia	70	M	None	Yoghurt, cheese, and milk	Biochemistry	Tazobactam/piperacillin (3 days) → moxifloxacin (3 weeks)	Recovered	Buchelli-Ramirez (2013)	Spain	32
Others										
Canaliculitis	80	F	Diabetes mellitus	None	Biochemistry	Ampicillin (oral) + chloramphenicol (topical)	Recovered	Leung (2006)	China	33
Septic arthritis	57	F	NA	Unpasteurized milk	NA	Penicillin (6 weeks)	Joint deformity	Campbell (1993)	UK	34
Urinary tract infection	0	M	Prematurity	Breast milk (*L. lactis* positive)	16S rRNA	Vancomycin + cefotaxime (4 days) → penicillin (1 day) → cefotaxime (2 days)	Recovered	Newby (2014)	Canada	35

NA: not available, CAPD: continuous ambulatory peritoneal dialysis, CLL: chronic lymphocytic leukemia, 16S rRNA: 16S ribosomal RNA sequencing, MALDI-TOF MS: matrix-assisted desorption/ionization time-of-flight mass spectrometry.

L. lactis infections have rarely been reported. A search for the English abstracts in the MEDLINE database revealed only 36 cases of human infection, including our case (Table 2). The median age of the reported cases was 46 years (range, 0–80 years). Endocarditis was the most common diagnosis (n = 8), followed by hepatobiliary infection (n = 6), central nervous system (CNS) infection (n = 5), and peritonitis (n = 4).

Underlying disorders can be associated with *L. lactis* infection. Underlying conditions were documented in 34 of the 36 reported cases; 24 of them involved significant underlying conditions. Thus, significant underlying conditions were present in 66.7% of the reported cases. Among these 24 patients with significant underlying conditions, 15 were considered to be immunocompromised; four had diabetes mellitus, four received peritoneal dialysis (including two diabetes patients), three had malignancy, three were premature infants, two were malnourished, and one was infected with human immunodeficiency virus (HIV). An immunocompromised state may be a predisposing factor for *L. lactis* infection. None of the 8 cases of endocarditis involved immunocompromised patients [2–9]. Three cases had intracardiac anatomical abnormalities (rheumatic fever, atrial myxoma, and mitral valve repair) [2,4,9], while one case had undergone root canal treatment before the onset of endocarditis [3].

Exposure to raw milk or unpasteurized dairy products are known to be risk factors for *L. lactis* infection. This is because *L. lactis* colonizes the mucocutaneous surface of bovines and is used to produce dairy products. For example, “Caspian Sea Yogurt”, a viscous fermented milk that is widely consumed in Japan, also contains *L. lactis*. A food consumption history was documented in 33 of the 36 cases, 15 of which involved a significant food consumption history, which accounted for 41.7% of all cases. All four cases of *L. lactis* peritonitis were associated with continuous ambulatory peritoneal dialysis (CAPD) and thus involved a significant food consumption history. CAPD peritonitis is mainly caused by gram-positive organisms colonizing the skin surface of the patient. Previous reports have identified the main route of infection as being direct intraluminal spread caused by contaminated hands [20–23]. In our case, the patient denied consuming unpasteurized milk or dairy products; thus, the route of infection was not proven.

The selection of antibiotics and the duration of treatment varied in the reported cases. Penicillin or vancomycin were used for definitive treatment in some cases. Penicillin plus a β-lactamase inhibitor or other broad-spectrum antibiotics were used in other cases. There may be some reasons for these variations. First, no definitive breakpoints for *Lactococcus* spp. are available and the optimal choice of treatment remains to be determined. Second, many cases were complicated by abscess formation and could be polymicrobial infections. Hence, broad-spectrum antibiotics were used for a long period in some cases. In our case, MIC for penicillin was lower than the breakpoint according to M45-A3, and MIC for ceftriaxone was low. However, CLSI M45-A3 did not show any breakpoint for cephalosporines [37]. Hence, we selected sulbactam/ampicillin in order to target *L. lactis* and other enteric bacteria. In addition to the administration of antibiotics, the performance of endoscopic biliary drainage was found to be very effective in our case. The duration of therapy ranged from 20 to 57 days for endocarditis, from 14 to 45 days for hepatobiliary infections, 15–93 days for CNS infections, 14–24 days for peritonitis, and 10–14 days for bacteremia and catheter-related bloodstream infections. The duration of therapy was usually extended in cases complicated with abscess formation; namely, from 22 to 45 days for a liver abscess, 40–73 days for an abscess in the CNS, and 42 days for a neck abscess. We provided 14 days of antimicrobial treatment according to the recommendations in Tokyo Guidelines for acute cholangitis and acute cholecystitis (TG13) [40].

The prognosis was favorable in most cases. The outcome was documented in 33 cases. A fatal outcome was seen in one case, and severe sequelae (joint deformity) were observed in another case. Although *L. lactis* and *Enterococcus faecalis* have similar biological features and antimicrobial susceptibilities [41], the reported mortality rate of enterococcal bacteremia (24.8–30.3%) is substantial [42,43]. This difference suggests *L. lactis* may be less pathogenic than *E. faecalis*.

Our case suggests MALDI-TOF MS can be useful for the rapid identification of *L. lactis*. The incidence of *L. lactis* infection may be underestimated due to several technological limitations. First, the identification of *Lactococcus* spp. is often challenging because it requires nutritionally rich media. Second, *Lactococcus* spp. may be misidentified as *E. faecalis* by commercially available test kits because both have similar morphologic and biochemical features [44]. In our literature review, the identification method was documented in 23 cases. Among these, a biochemical identification method was used in the 17 cases and 16S rRNA sequencing was performed in 5 cases. Tanigawa et al. reported that MALDI-TOF MS, a novel tool to analyze whole-cell protein patterns that enables the identification of rare microorganisms, can identify *Lactococcus* spp. as accurately as genotypic identification methods [45]. They also stated that MALDI-TOF MS (Voyager-DE PRO; Applied Biosystems, Foster City, CA, USA) can discriminate *L. lactis* subsp. *cremoris* from *L. lactis* subsp. *lactis*. In our case, *L. lactis* was identified by MALDI-TOF MS but the detailed species was not determined because the MALDI-TOF MS apparatus was different from the one used in the abovementioned study.16S rRNA sequencing was not performed in the present study because the isolate was considered to have been correctly identified based on the high confidence score (2.339).

In conclusion, we encountered a case of *L. lactis* cholangitis complicated by cholangiocarcinoma. Our case suggests that *L. lactis* is a potential pathogen of cholangitis and that MALDI-TOF MS can be useful for the rapid and accurate identification of *L. lactis* infection. Our review of the pertinent literature showed that *L. lactis* can be a causative organism of various infections; however, *L. lactis* infection is associated with relatively low rates of mortality and morbidity. Two thirds of the cases had underlying conditions and approximately half of the cases had a significant food consumption history.

Conflicts of interest

The authors declare no conflicts of interest in association with the present study.

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Ethical approval

Informed consent was obtained from the patient's wife for publication of this case report. This report was approved for publication by the ethical committee of Kameda Medical Center.

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