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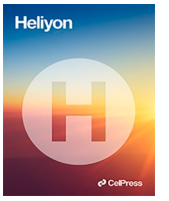

Pyogenic liver abscess associated with *Klebsiella oxytoca*: Mimicking invasive liver abscess syndrome

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ABSTRACT

A pyogenic liver abscess (PLA) is a space-occupying lesion in the liver that is associated with significant morbidity and mortality. We herein present the case of a Japanese 76-year-old man who visited our hospital with fever and back pain lasting 3 weeks after endoscopic treatment for common bile duct stones. He was accompanied by poorly controlled diabetes mellitus (DM) with an HbA1c of 9.7 %. Laboratory tests disclosed elevated C-reactive protein level (22.1 mg/dL) and white cell count (11,910/μL). Abdominal computed tomography (CT) revealed hypodense lesions in the right liver lobe, with abdominal ultrasonography showing an echogenicity-mixed hypoechoic lesion. Percutaneous needle aspiration of a liver lesion was performed under suspicion of a PLA. Subsequent enhanced CT and magnetic resonance imaging confirmed the hepatic lesions in the right lobe as well as a septic pulmonary embolism, right hepatic vein thrombosis, spondylodiscitis, and a retroperitoneal abscess. Gram staining of the abscess drainage revealed gram-negative bacteria. The above findings indicated invasive liver abscess syndrome (ILAS) caused by *Klebsiella pneumoniae*. However, further examination of blood, urine, and abscess drainage cultures revealed positivity for *Klebsiella oxytoca*. This case illustrates that *K. oxytoca* may cause ILAS-like symptoms. Screening for systemic metastatic infection should be considered in patients with PLA due to *K. oxytoca* in whom therapeutic intervention has been delayed, especially in patients with poorly controlled DM.

1. Introduction

Invasive liver abscess syndrome (ILAS) is a clinical condition characterized by the presence of a pyogenic liver abscess (PLA) caused by *Klebsiella pneumoniae* along with such extrahepatic complications as endophthalmitis, meningitis, necrotizing fasciitis, and spondylodiscitis [1,2]. *Klebsiella* is a gram-negative, anaerobic, rod-shaped enterobacterium known to attack immune-compromised patients [3]. This opportunistic pathogen is widely distributed and often has a commensal presence in the human nasopharynx and intestinal tract, animal bowel, water, and soil [4]. Among the *Klebsiella* species (spp), *Klebsiella oxytoca* is second only to *K. pneumoniae* in frequency of isolation. *K. oxytoca* can cause a wide range of diseases, including colitis and infective endocarditis, as well as common

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urinary tract and respiratory tract infections [5]. However, there are few reports of *K. oxytoca* being detected in liver abscesses, with no cases as the metastatic focus of infection.

This report describes the case of a PLA caused by *K. oxytoca* resulting in a septic pulmonary embolism, right hepatic vein thrombosis, spondylodiscitis, and a retroperitoneal abscess, which presented symptoms similar to those in ILAS.

1.1. Case report

A 76-year-old Japanese man was admitted to our hospital for endoscopic treatment of common bile duct stones. Endoscopic retrograde cholangiopancreatography confirmed a filling defect within the lower common bile duct. The stones were extracted from the common bile duct during endoscopic sphincterotomy using balloon sweep. One week after discharge, he suffered fever and back pain that persisted for 3 weeks. The fever rose to 39.1 °C, but the patient self-medicated with an over-the-counter antipyretic. The patient was seen in the outpatient clinic on the originally scheduled date. He had a history of diabetes mellitus (DM) and hypertension and was taking several oral medications, including cilnidipine and metformin hydrochloride. He had no known allergies, but reported smoking 20 cigarettes per day for 47 years and consuming 70 g of ethanol daily in that period. His height, weight, and body mass index were 168 cm, 54 kg, and 19.2 kg/m^2, respectively. Upon admission, physical examination showed a temperature of 37.8 °C with normal vital signs. The liver was not tender and was not palpable. There was no evidence of endocarditis, including heart murmur, Osler's nodes, or Janeway lesions. No tenderness was noted upon palpation of the spine or bilateral costovertebral angles. Furthermore, there were no indications of muscle weakness or sensory impairments, and the Straight Leg Raise test yielded negative results bilaterally.

Laboratory findings revealed elevated C-reactive protein (CRP) level (22.1 mg/dL) and white cell count (11,910/μL) along with low platelet count (10.3 × 10^4/μL). His serum aspartate aminotransferase level was normal at 15 U/L, alanine aminotransferase was normal at 14 IU/L, alkaline phosphatase was elevated at 275 U/L, and gamma-glutamyltranspeptidase was normal at 20 U/L. His serum albumin level was low at 1.7 g/dL. Renal function and coagulation capacity were within normal limits. Fasting blood glucose of 280 mg/dL and HbA1c of 9.3 % indicated poorly controlled DM. T-SPOT Mycobacterium tuberculosis-specific IFN-γ, HBs antigen, anti-HCV antibody, and anti-HIV antigen/antibody were all negative. The string test was negative. The tumor markers CEA, CA19-9, AFP, and PIVKA-2 were all within normal range (Table 1).

Abdominal computed tomography (CT) revealed 2 hypodense lesions in the right liver lobe (Fig. 1a), while abdominal ultrasonography detected an echogenicity-mixed hypoechoic lesion (Fig. 1b). These imaging findings did not suggest any signs of biliary tract illness, including biliary obstruction, gallstones, or gallbladder wall thickening. Under suspicion of a PLA, percutaneous needle aspiration of the liver lesion was performed for microbiological examination. The patient was started on cefoperazone/sulbactam (2.0 g/day) following re-admission. Subsequent enhanced CT and magnetic resonance imaging uncovered a septic pulmonary embolism (Fig. 2a), right hepatic vein thrombosis (Fig. 2b), a retroperitoneal abscess (Fig. 3a) and spondylodiscitis (L4/5) (Fig. 3b) in addition to the hepatic lesions in the right lobe.

Gram staining revealed gram-negative bacilli, leading to the assumption that the patient's findings were due to ILAS caused by a PLA from *K. pneumoniae*. The antibiotic was changed to cefmetazole (4 g/day) and anticoagulant therapy with edoxaban tosilate hydrate (30 mg/day) was initiated. Intraocular and echocardiographic examination to rule out *Klebsiella* endophthalmitis and tricuspid

Table 1
Laboratory data on admission.

Hematology			Biochemistry					
WBC	11910	/μL	TP	4.8	g/dL	HbA1c	9.3	%
Neu	93.2	%	Alb	1.7	g/dL	CRP	22.1	mg/dL
Lym	3.5	%	AST	15	U/L			
Eosino	0.1	%	ALT	14	U/L	**Infection marker**		
RBC	348 × 10^4	/μL	ALP	275	U/L	B-D glucan	-	
Hemoglobin	10.7	g/dL	γ-GTP	20	U/L	T-SPOT	-	
HCT	30.6	%	T-Bil	1.18	mg/dL	HIV-Ab/Ab	-	
MCV	87.9	fL	BUN	18.7	mg/dL	HBs-Ag	-	
Platelet	10.3 × 10^4	/μL	Cre	0.87	mg/dL	HCV-Ab	-	
			Na	135	mEq/L			
Coagulation			K	2.7	mEq/L			
PT-INR	1.17		Cl	98	mEq/L			
APTT	34.7	sec	Glucose	280	mg/dL			

Alb, albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cre, creatinine; CRP, C-reactive protein; Eosino, Eosinophils; GGTP, gamma-glutamyl transpeptidase; HbA1c, hemoglobin A1c; HCT, hematocrit; Lym, lymphocytes; MCV, mean corpuscular volume; Neu, neutrophils; PT-INR, prothrombin time-international normalized ratio; RBC, red blood cells; T-Bil, total bilirubin; TP, total protein; WBC, white blood cells.

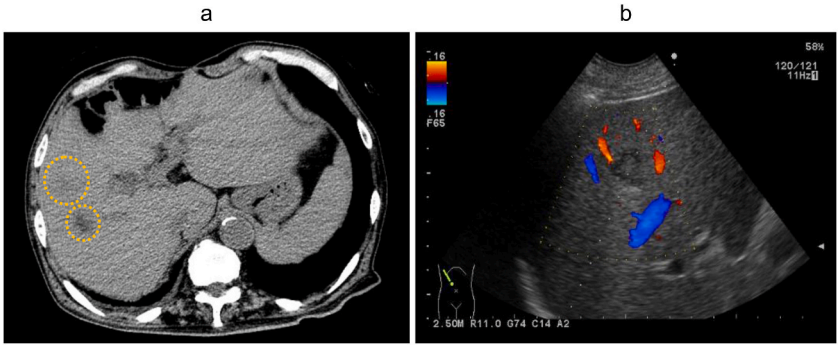

Fig. 1. (a) Abdominal computed tomography revealed 2 hypodense lesions in the right liver lobe (yellow circles). (b) Doppler abdominal ultrasonography showed an echogenicity-mixed hypoechoic lesion without blood flow.

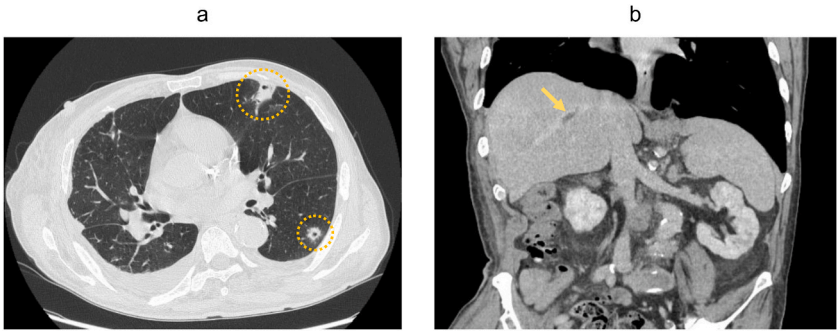

Fig. 2. (a) Chest computed tomography detected multiple cavitated nodules (yellow circles). (b) Enhanced abdominal computed tomography showed thrombosis of the hepatic vein (yellow arrow).

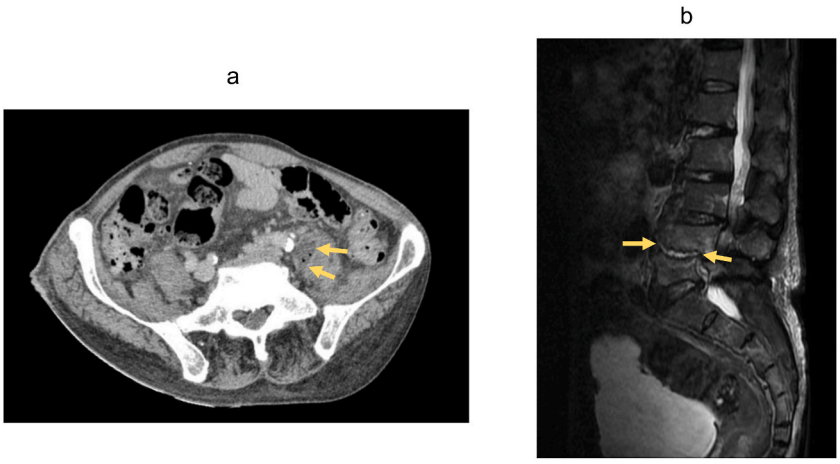

Fig. 3. (a) Abdominal computed tomography showed a low-density area of left-sided iliopsoas muscle swelling (yellow arrow). (b) Short tau inversion recovery magnetic resonance imaging depicted enlarged high-signal areas in the L4/5 intervertebral disc (yellow arrow) and in the upper and lower vertebral bodies.

valve warts, respectively, were negative. Unexpectedly, aspirated abscess fluid, blood, and urine cultures taken on admission were all positive for *K. oxytoca*. MALDI-ToF mass spectrometry (Bruker Daltonics, Bremen, Germany) employing the BDAL 9.0 database was used for identification of bacterial species. Results of antimicrobial susceptibility of *K. oxytoca* are shown in Table 2.

After receiving antibiotics and anticoagulants, the patient's back pain improved, and his elevated CRP and fever decreased (Fig. 4). On the 25th day of hospitalization, CT and abdominal ultrasonography showed reduction of the lung lesion and retroperitoneal abscess and disappearance of the right hepatic vein thrombus. Anticoagulation treatment was discontinued, and the patient was transferred to

Table 2
Antimicrobial susceptibility of *Klebsiella oxytoca*.

Antimicrobial agent	MIC (mg/mL)	SIR result
Ampicillin	>16	R
Ampicillin/sulbactam	8	S
Amoxicillin/clavulanic acid	≦ 8	S
Piperacillin	16	S
Piperacillin-tazobactam	≦ 8	S
Cefazolin	>16	R
Cefmetazole	≦ 16	S
Ceftriaxone	≦ 1	S
Cefepime	≦ 2	S
Cefoperazone/sulbactam	≦ 16	S
Meropenem	≦ 1	S
Amikacin	≦ 4	S
Sulfamethoxazole-trimethoprim	≦ 2	S
Levofloxacin	≦ 0.5	S

Susceptibility testing of K. oxytoca was performed according to Clinical and Laboratory Standards Institute (CLSI) document (ver. 26).
I, intermediate; MIC, minimum inhibitory concentration; R, resistant; S, susceptible.

his referring physician. After the hospital transfer, he received antibiotic therapy with levofloxacin (500 mg/day) for a total of 8 weeks based on the antimicrobial susceptibility (Table 2), with no symptom flare-ups.

We searched the English literature using the terms "liver abscess" and "*Klebsiella oxytoca*" in PubMed/MEDLINE and retrieved 10 relevant references. While 4 reports included the finding of liver abscess caused by *K. oxytoca* [6–9], none of them described symptoms such as ILAS that were associated with metastatic infection (Table 3).

2. Discussion

We successfully managed a patient with a PLA caused by *K. oxytoca* that led to a septic pulmonary embolism, right hepatic vein thrombosis, spondylodiscitis, and a retroperitoneal abscess. To the best of our knowledge, this is the first report of a PLA caused by *K. oxytoca* presenting with metastatic infection similar to that of ILAS.

In a study of 540 cases of intra-abdominal abscesses including intra- and retroperitoneal lesions, liver abscesses made up 13 % of all intra-abdominal abscesses and 48 % of visceral abscesses [10]. The incidence of intra-abdominal abscesses varies significantly by region, ranging from 3.6 to 13.52 per 100,000 individuals in Taiwan, Germany, and United States [11–13]. The most common underlying diseases are reportedly DM (35.3 %), cholelithiasis (13.1 %), and hepatocellular carcinoma (9.8 %) [14].

In *K. pneumoniae*, K1/K2 serotypes, hypermucoviscosity, and expression of the magA gene are strongly related to high virulence [15,16]; K1/K2 serotypes and expression of the magA gene lack the capsular sugar sequences recognized by macrophages [17], while hypermucoviscosity causes increased resistance to complement-mediated serum killing [18]. Therefore, a certain number of individuals with a PLA caused by *K. pneumoniae* display ILAS symptoms. ILAS was first reported in Taiwan in the 1980s [19]. Subsequently, a considerable number of cases have been confirmed in East Asian countries. Several cases have also been reported in the Americas, with the same characteristics as those reported in Asia, confirming the worldwide spread of the disease [20]. Endophthalmitis, meningitis, and brain abscess are the most typical symptoms of ILAS [14,21]. Other signs include psoas abscess, lung abscess, spondylodiscitis, and septic pulmonary emboli [2,11,22]. Patients afflicted with liver abscesses resulting from *Klebsiella* spp. may experience thrombophlebitis within the hepatic venous system, which is considered a plausible cause of septic pulmonary embolism [23]. ILAS is prone to misdiagnosis due to non-specific symptoms, atypical presentations, overlapping clinical conditions, and lack of awareness. To reduce misdiagnosis in ILAS, health care providers should increase awareness of ILAS, utilize advanced imaging techniques, and ensure invasive access to the abscess area when necessary.

The major surface antigens of *Klebsiella* spp. are capsular polysaccharide (CPS; K antigen) and lipopolysaccharide (LPS; containing O antigen), which are common virulence factors of *K. pneumoniae*. Interestingly, recent reports of genome analysis indicate that the O and K antigen types of *K. oxytoca* overlap with those of *K. pneumoniae* [24]. However, a definitive association between *K. oxytoca* and ILAS by *K. pneumoniae* has not been established in the existing literature. It is also important to note that in the present case, the infection was prolonged without effective treatment after endoscopy, which may have enhanced the infectivity of *K. oxytoca* regardless of its intrinsic virulence. Further studies are needed to determine the exact mechanism of invasive infection by *K. oxytoca.*

K. oxytoca is a commensal bacterium and was not recognized as a common pathogen of bacteremia. However, numerous studies and cases of bacteremia caused by *K. oxytoca* in patients of all ages have recently been reported [5,25]. Most *K. oxytoca* bacteremia cases are associated with certain underlying diseases, such as DM, malignancy, chemotherapy, chronic obstructive pulmonary disease, and chronic renal failure [5,25]. Furthermore, the majority of *K. oxytoca* bacteremia was secondary to infection of other sites, with hepatobiliary infection (58 % of patients) being the most common original site of infection [26]. Considering these characteristics of *K. oxytoca* bacteremia, it is highly likely that the present case had bacteremia secondary to hepatobiliary infection with *K. oxytoca* in a diabetic background.

A possible mechanism of thrombus formation in vascular vessels includes increased coagulability caused by endotoxin from

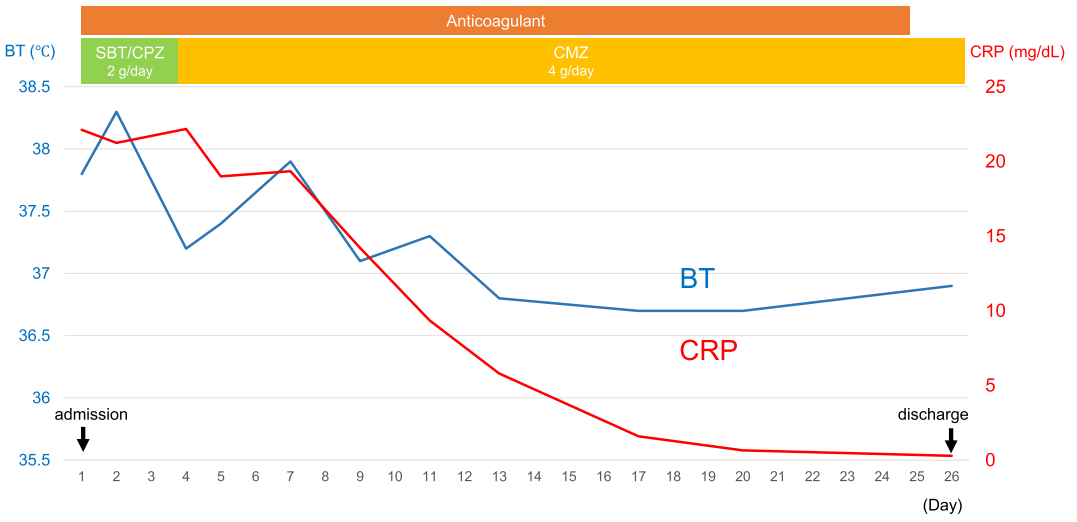

Fig. 4. Clinical course. BT, body temperature; CRP, C-reactive protein.

Table 3
Reported cases of liver abscess caused by *Klebsiella. oxytoca.*

No	Case	Diabetes mellitus	Background	References
1	64, Male	+	Cholecystitis	Paasch C et al
2	80, Male	+	Cholangitis/Endoscopic procedure	Lee JY et al
3	84, Male	-	Liver cyst	Surani A et al
4	74, Male	-	Cholelithiasis/Cholecystectom	Osório C et al
This case	76, Male	+	Choledocholithiasis/Endoscopic procedure	

K. oxytoca and blood flow stagnation due to venous drainage of the liver abscess. In this case, the liver abscess was in contact with the right hepatic vein and the thrombus was continuously formed at the same site, suggesting that direct spillover of inflammation into the vein was the main cause of the thrombus.

In conclusion, we need to recognize that *K. oxytoca* can cause ILAS-like symptoms and that a systematic search for metastatic infection should be considered in patients with PLA due to *K. oxytoca*, especially in poorly controlled DM patients with delayed treatment initiation.

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Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Takanobu Iwadare: Conceptualization, Data curation, Investigation, Writing – original draft. **Takefumi Kimura:** Conceptualization, Data curation, Investigation, Writing – review & editing. **Ayumi Sugiura:** Writing – review & editing. **Risa Takei:**

Investigation. **Masato Kamakura:** Investigation. **Shun-ichi Wakabayashi:** Investigation. **Taiki Okumura:** Investigation. **Daichi Hara:** Investigation. **Akira Nakamura:** Supervision. **Takeji Umemura:** Funding acquisition, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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