The increased recurrence rate of liver abscess caused by extended-spectrum β-lactamase-producing Klebsiella pneumoniae

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Research article

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Abstract

Background The pathogenic bacterium Klebsiella pneumoniae (KP) is the major causative agent of pyogenic liver abscess (PLA). But reports about the prognosis of KP-caused PLA (KPLA) are rare. This study aimed to ascertain the recurrence rate of KPLA after initial treatment, and its contributing factors.

Methods The medical records data were retrospectively analyzed of KPLA patients who were admitted to Shengjing Hospital of China Medical University from January 2012 to January 2018. According to whether or not there was recurrence of KPLA during follow-up, the patients were divided into a 'recurrence' and a 'non-recurrence' group. The clinical and CT characteristics of patients were compared between the two groups, and those factors related to KPLA recurrence were further analyzed.

Results A total of 110 patients who had first-time episodes of KPLA were included into the study. The average follow-up time was 3.65±2.18 years. Twenty (18.18%) KPLA patients experienced recurrence. Those in the recurrence group had a significantly greater incidence of extended-spectrum β-lactamase (ESBL) production compared to the non-recurrence group (30.0% vs 8.89%, P=0.018). Diabetes, biliary tract disease, and history of malignancy was not associated with recurrence (all P>0.05). No difference in the CT characteristics of KPLA (including abscess size, location, whether multilocular, gas production of KPLA, and thrombophlebitis) was found between the two groups. Multivariate regression analysis showed that ESBL production (OR, 6.3; 95% CI, 1.02–38.59; P=0.04) was an independent risk factor for the recurrence of KPLA.

Conclusions KPLA has a high recurrence rate, and ESBL production is a risk factor for recurrent KPLA.

Background

Klebsiella pneumonia-caused pyogenic liver abscess (KPLA) was first discovered in the 1980s in Taiwan and successively reported in mainland China and, as reported cases gradually increased, other countries[1–5]. At present, Klebsiella pneumonia (KP) is the major causative pathogenic bacterium of liver abscess in China[2–4, 6, 7]. KP is part of the normal flora colonizing the human intestine but readily causes extra-intestinal infection and even bacteremia under conditions of poor or compromised immunity[8]. The liver is the most common extra-intestinal organ to be infected. With the development of interventional radiology technology in recent years, the combination of percutaneous puncture drainage and antibiotics has become the mainstay of therapy which, compared to antibiotics therapy alone and surgical treatment, causes little trauma and has significant efficacy[9, 10].

Diabetes, biliary tract disease, and history of malignancy are the currently recognized pathogenic precursors of pyogenic liver abscess (PLA)[11, 12]. Past study has shown that PLA patients with biliary tract disease are particularly susceptible to recurrence of the disease[12]. However, to date there have been no separate reports on the recurrence rate of KPLA and its contributing factors.

In this study, the medical records data of patients who had had an episode (their first) of KPLA were retrospectively analyzed according to whether or not they experienced a recurrence of the condition. Thus, the patients were divided into a recurrence group and a non-recurrence group. The clinical and CT characteristics of patients were compared between the two groups, and the factors contributing to recurrence were further analyzed.

Methods

Patient population

The Ethics Committee in Shengjing Hospital of China Medical University granted approval for this retrospective study, with a waiver of informed consent because the medical records of the subjects were de-identified to ensure patient confidentiality. Using our institutional electronic medical database, we retrieved the records of patients given the principal diagnosis of liver abscess between January 2012 and January 2018.

The inclusion criteria were: (a) presence of a focal lesion or lesions in the liver as shown on contrast enhanced CT images; (b) frank pus aspirated from the abscess cavity through diagnostic, and/or surgical drainage procedures; (c) positive microbiological culture results from liver abscess and/or blood cultures; and (d) monomicrobial K. pneumoniae shown on culture.

The review of the clinical and laboratory data of the patients included the following: (1) sex and age; (2) potential diseases; (3) primary clinical symptoms; (4) results of laboratory examinations, such as white blood cell count, platelet count, total bilirubin, alanine aminotransferase level, albumin level, and C-reaction protein level; and (5) whether the patient was admitted to the intensive care unit (ICU) and number of days of hospitalization.

CT Characteristics

All patients underwent contrast-enhanced CT of the liver before drainage of the liver abscess[6, 13]. The contrast-enhanced CT images were reviewed for the purpose of this study. The scans were reviewed by two radiologists who reached agreement between them. The following features were recorded: (a) lobe involvement (unilobar [right or left] or bilobar); (b) number of abscesses (single or multiple); (c) maximal abscess diameter, with the largest abscess measured when there were multiple abscesses; (d) unilocular or multilocular (presence of ≥1 mm-thick septations); (e) solid or cystic appearance (cystic defined as >50% of the abscess cavity appearing hypodense or liquefied, with an attenuation value of ≤20 HU) in most of the sections showing the abscess cavity, (f) gas within the abscess cavity; (g) thrombophlebitis (hypodense filling defects in the contrast-enhanced hepatic veins, their tributaries, and/or the inferior vena cava); and (h) spontaneous rupture of the abscess (based on CT and clinical symptoms).

Treatment

Same as our previous reports[6, 13, 14]. Briefly, in addition to percutaneous drainage therapy, all patients received antibiotic therapy (most commonly third-generation cephalosporins, ciprofloxacin, or carbapenem antibiotics) for their abscesses.

Microbiologic data

Both aerobic and anaerobic cultures were performed on the pus samples. Species identification and antimicrobial susceptibility were tested using the VITEK automated systems (bioMérieuxVitek, USA), and interpreted according to guidelines established by the Clinical and Laboratory Standards Institute (CLSI) according to the CLSI criteria. Phenotypic confirmation of ESBL detection was performed using the double-disk diffusion method in our clinical microbiology laboratories, as recommended by the CLSI[15].

Definitions and follow up

Patients' enrolment in the study ended if/when their liver abscess recurred, if they died, or were lost to follow up. The recurrence of liver abscess was defined as presenting with a typical clinical presentation, with new CT findings of abscess recurrence after the first episode of KPLA had been fully cured, regardless of whether or not the pus or blood bacterial culture result showed KP in the 2nd episode. 'Cure' was defined as the absence of clinical signs and symptoms together with negative blood cultures and image studies. However, if the patients had recurrent clinical symptoms within 1 month of discharge in a similar location as occurred with the previous liver abscess (irrespective of abscess size or numbers), such patients were then noted as having a relapse due to incomplete treatment. These patients were not defined as having a recurrence of their liver abscess.

Statistical Analysis

Statistical analyses were performed using SPSS software (Version 22; SPSS Inc, Chicago, Ill). Data are expressed as mean±SD for continuous variables and percentage for categorical variables. The $\chi 2$ test or Fisher exact test was used for categorical variables and the independent sample t test was used for continuous variables.

The statistically significant independent factors obtained by univariate analyses and underlying diseases related to the pathogenesis of liver abscess were entered into a multiple logistic regression model to

identify independent risk factors for KPLA recurrence. Statistical significance was considered to have been achieved when P< 0.05.

Results

Demographic characteristics

A total of 110 patients with a past initial episode of KPLA were included in the study, and the follow-up period was 3.65±2.18 years on average. The follow-up results showed that 20 cases experienced recurrence of KPLA. The incidence of patients with ESBL production was significantly greater in the recurrence group than in the non-recurrence group (30.0% vs 8.89%, P=0.018). There was no difference between two groups in the percentages of patients with diabetes, biliary tract disease or history of malignancy (all P>0.05). Moreover, there was no difference in the hospital stay and ICU admission rates between the two groups (Table 1).

Laboratory findings

Table 2 shows a comparison of the laboratory data between the two groups. There were no significant differences in the white blood cell count (P=0.61), platelet count (P=0.25), hemoglobin (P=0.51), total bilirubin (P=0.84), albumin (P=0.78), prothrombin time (P=0.89), or creatinine (P=0.07). The C-reactive protein (CRP) and D-dimer were lower in the recurrence patients, although neither were significantly different (P□0.05).

Liver CT characteristics

The characteristics of the liver abscesses are summarized in Table 3. A single abscess was found in 71 (64.55%) patients, and multiple abscesses were seen in 39 (35.45%) patients. Among those patients with multiple abscesses, the average number of lesions per patient was 2.3±0.7. Multilocular abscess was present in 78 (70.91%) patients. The abscesses were predominantly solid in 58 (52.73%) patients. Thrombophlebitis was present in 9 (8.18%) patients, and gas in the abscess cavity was present in 20 patients (18.18%). There were 7 (6.36%) patients with liver abscess who experienced a spontaneous rupture of the abscess. However, there was no statistical difference between the recurrence group and non-recurrence group in these CT characteristics.

Risk factor analyses

The logistic multivariate regression analysis results suggested that none of the following were associated with the recurrence of KPLA: diabetes (OR, 0.84; 95% CI, 0.26–2.67; P =0.77) biliary tract disease (OR,

0.81; 95% CI, 0.19–3.44; P=0.78), and history of malignancy (OR, 1.01; 95% CI, 0.28–3.58; P=0.51). Only ESBL production (OR, 6.3; 95% CI, 1.02–38.59; P=0.04) was found to be an independent risk factor for recurrent KPLA (Table 4).

Discussion

This study demonstrates that the recognized potential etiological factors of liver abscess, such as diabetes, biliary tract disease and malignancy history, are not risk factors for the recurrence of KPLA, and that ESBL production is a risk factor for the recurrence of KPLA. Czerwonko ME et al. have shown that multidrug resistant of bacteria is an independent risk factor for PLA recurrence[12]; this is in concordance with our study conclusion, though there was no separate investigation of ESBL production and KPLA in their study. ESBL-producing bacteria are resistant to a broad range of beta-lactams including third-generation cephalosporins, presenting a huge clinical treatment challenge[16]. Past studies have revealed that morbidity rates increase in cases of KPLA with ESBL production[17-21]. The use of third-generation cephalosporins and fluoroquinolone antibiotics, long hospital stay, and concomitant diabetes may increase the incidence of ESBL production[17]. Therefore, it is critical to actively investigate possible causes of ESBL production so as to prevent KPLA recurrence in the future.

Ascending bacterial spread via the biliary tract is one of the main infection pathways leading to liver abscess; hence, cholelithiasis, cholangitis, post cholecystenterostomy and biliary stent implantation can all increase the likelihood of PLA morbidity[3, 7, 8, 22]. Recent studies have shown biliary tract disease to be associated with recurrence of KPLA[11, 22, 23], however, our study results did not reach this conclusion. Fewer patients with biliary tract disease in our study may account for this result. Other than KP, Escherichia coli is also predominant among the causative pathogenic bacteria of PLA, based on clinical experience and literature reports[16, 18]. In Yoon JH's study, patients with biliary tract disease accounted for 24.3% of Escherichia coli-caused liver abscess patients but only 8.3% of KPLA patients[23]. Our study included only 14 patients (12.7%) with biliary tract disease since only KPLA patients were included in our study.

A history of malignancy is also a risk factor for PLA, especially malignant gastrointestinal tumors[22, 24, 25]. KP can colonize the intestine and penetrate the intestinal mucosal barrier in pathological states to enter the liver via the portal vein system and subsequently cause PLA[1]. One study has even suggested that PLA is a potential early manifestation and predictive factor for colorectal cancer[26]. The prevalence rate of colorectal cancer is 7.9% in PLA patients, which is higher than control in a systematic review [27]. Our results however did not demonstrate a relation between history of malignancy and KPLA, perhaps due to the small number of patients with a history of malignancy in our study.

Numerous past studies have shown that diabetic patients are more susceptible to KPLA than are non-diabetic patients[28-30]. However, we did not find a correlation between diabetes and KPLA recurrence. Some studies have revealed that poor control of blood glucose makes the occurrence of KPLA more likely[28-30], and thus stricter control of blood glucose in KPLA patients post-treatment will undoubtedly

decrease the recurrence rate of KPLA. Diabetic patients with KP infection are more susceptible to other serious infections, such as pneumonia, meningitis and endophthalmitis, because of hypoimmunity, and the aggressive application of large amounts of antibiotics during treatment undoubtedly increases the risk of ESBL production. So, the relationship between diabetes and KP and ESBL production needs to be further studied.

In our previous study, the CT characteristics of KPLA were analyzed in depth. KPLA often presents as a solid, multilocular abscess, often complicated with thrombophlebitis[6]. In this study, we also explored whether the CT characteristics of KPLA could predict its recurrence. Our results however showed that various CT signs were not related to KPLA recurrence. CT signs are limited to reflect the morphological features of the abscess, not their clinical and microbiological characteristics. Radiomics may be more valuable for the purposes of analysis[31]. In another study of ours, the hosts' metabolic characteristics underwent nuclear magnetic resonance (NMR) analysis to evaluate the drainage resistance phenomenon of KPLA, and five key metabolites were identified which might be potential targets for guiding novel therapeutics[14]. This indicates that the occurrence and progress of a liver abscess could be further explored using functional imaging methods that can reflect metabolic characteristics, such as magnetic resonance spectroscopy and molecular imaging[32].

This study has some shortcomings. Firstly, the sample size was small, though it was the largest study to specifically investigate the factors influencing the recurrence of KPLA. Secondly, being a retrospective study, we were unable to systematically record the medications of patients after discharge. Therapeutic drugs administered for some chronic diseases may affect the recurrence of PLA; for example, studies have shown that aspirin can reduce the recurrence rate of PLA[24]. In addition, the patients in this study were all from a province in Northeastern China, and the epidemiology of KP may be influenced by geographic factors.

Conclusion

KPLA patients have a high recurrence rate, and ESBL production is a risk factor for KPLA recurrence. Diabetes, biliary tract disease and history of malignancy are not associated with the recurrence of KPLA.

Abbreviations

KP: Klebsiella pneumoniae; KPLA: Klebsiella pneumoniae liver abscess; PLA: pyogenic liver abscess; ESBL: extended-spectrum β-lactamase

Declarations

Acknowledgements

None

Authors' contributions

ZC wrote the manuscript and performed statistical analysis. YR and HW were

the principal investigators of the clinical data. ZC contributed to analysis and

discussion and wrote the paper. ZL designed the study, contributed to analysis and

wrote the paper. ZC, YR, HW and ZL reviewed and edited the manuscript. All authors read and approved the final manuscript

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Availability of data and materials

The data analyzed during this study are included in this paper. Some of the datasets are available from the corresponding author upon reasonable request.

Ethical Approval and consent to participate

Approval for the study was obtained from our Institutional Review Board and consent of the patients was waived due to the retrospective nature of the study.

Consent for publication

Not applicable.

Conflict of Interest

The authors declare that they have no competing interest.

Author details

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Tables

Table 1. Clinical Characteristics in 110 patients with Klebsiella pneumoniae liver abscess

	No recurrence （n=90）	Recurrence （n=20)	p
Age, years,	58.90±13.77	62.44±11.50	0.31
Sex, male, n (%)	47(52.22)	10(50.00)	0.54
Underlying disease			
Diabetes mellitus	41(45.56)	10 (50.00)	0.43
Malignancy	9(10.00)	4(20.00)	0.18
Biliary tract disease	11(12.22)	3(15.00)	0.41
Cryptogenic	22(24.44)	4(20.00)	0.38
Presenting symptoms			
Fever (≥385◦C)	61(67.78)	13(65.00)	0.53
Abdominal pain/discomfort	14(15.56)	5(25.00)	0.23
Gastrointestinal symptoms	22(24.44)	5(25.00)	0.57
ICU admission	6(6.67)	0	0.29
ESBL production	8(8.89)	6(30.00)	0.018
Days of hospitalization	9.46 ± 3.53	10.32±4.66	0.52

Table 2Laboratory findings of of 110 patients with Klebsiella pneumoniae liver abscess

	No recurrence （n=90）	Recurrence （n=20)	p
CRP (mg/L)	181.82±108.19	134.84±53.34	0.21
D-dimer	2001.09±2904.43	1360.42±1519.54	0.42
Creatinine	68.98±23.60	86.42±64.77	0.07
Total bilirubin	18.31±16.69	17.51±8.81	0.84
Albumin	30.28±5.78	30.71±5.44	0.78
Platelet	239.00±136.51	198.94±114.51	0.25
Hemoglobin	117.31±21.18	113.66±20.882	0.51
White blood cell	10.77±5.91	10.43±4.76	0.61
PT	15.18±0.89	15.21±0.59	0.89

Table 3. CT Findings of 110 patients with Klebsiella pneumoniae liver abscess

CT Findings	No recurrence (n=90)	Recurrence (n=20)	*p*
Maximal abscess diameter(mm)	68.26 ± 19.77	72.55 ±22.12	0.33
Spontaneous rupture	6 (6.67)	1(5.00)	0.46
Thrombophlebitis	7(7.78)	2(10.00)	0.36
Single	59(65.56)	12(60.00)	0.42
Multilocular	65(72.22)	13(65.00)	0.35
Gas formation	16(17.78)	4(20.00)	0.50
Solid	50(55.56)	8(40.00)	0.25
Bilobular involvement	8(8.89)	1(5.00)	0.49

Table.4 Multivariable odds ratios (ORs) and 95% confidence intervals (CIs) for recurrence.

	B	OR (95 CI)	p
Diabetes mellitus	-0.167	0.84(0.26-2.67)	0.77
Malignancy	0.614	1.01 (0.28-3.58)	0.51
Biliary tract disease	-0.205	0.81 (0.19-3.44)	0.78
ESBL production	1.84	6.3(1.02-38.59)	0.04