

Pyogenic Liver Abscess and Endogenous Endophthalmitis Due to K64-ST1764 Hypervirulent *Klebsiella pneumoniae*: A Case Report

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Rationale: *Klebsiella pneumoniae* (*K. pneumoniae*, KP) are divided into two types: classic *K. pneumoniae* (cKP) and hypervirulent *K. pneumoniae* (hvKP). hvKP causes liver abscess and metastatic infection. Here, we report one case with pyogenic liver abscess (PLA) and endogenous endophthalmitis (EE) due to a relatively rarely reported serotype of *K. pneumoniae* in China.

Patient Concerns: An 80-year old man presented with nausea, vomiting, and epigastric discomfort for 2 weeks.

Diagnoses: PLA was identified by CT scan and abdominal ultrasound. Urgent ophthalmologic consultation was performed. B-scan ocular ultrasound was done and he was diagnosed as EE.

Interventions: Antibiotic treatment, intravitreal injection of eyes and eye drops were given. Percutaneous needle aspiration, evisceration, and drainage of the right eye were performed.

Outcomes: Cultures of the blood, the aspirated pus from the liver abscess, and the contents of the eyeball all yielded *K. pneumoniae* with a positive string test. The capsular serotype was K64. According to the existence of multiple virulence genes and the severe invasive clinical manifestation, this strain is regarded as a hvKp strain. Multilocus sequence typing (MLST) revealed the sequence type (ST) of this strain was K64-ST1764. Antimicrobial resistance genes, *bla*_{NDM-1} and *bla*_{KPC-2}, were not detected in the genome. The patient lost his eyesight but his symptoms subsided. During 15 months follow-up, the result was satisfactory.

Lessons: Here, we report one case with PLA due to a relatively rarely reported serotype of *K. pneumoniae* in China. This K64 *K. pneumoniae* strain is confirmed as hvKp by multiple methods. It is noteworthy that the sequence type is K64-ST1764 instead of the commonest ST11. Moreover, this strain is not considered a *K. pneumoniae* carbapenemase-producing *K. pneumoniae* (KPC-Kp) or a carbapenem-resistant *K. pneumoniae* (CRKP) as it is usually. Further follow-up and research are required to investigate this strain.

Keywords: case report, hypervirulent *Klebsiella pneumoniae*, pyogenic liver abscess, antibiotic resistance, ultrasonography guided puncture aspiration

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Introduction

PLA is a potentially life-threatening disease which is mainly caused by bacteria. Along with the increasing prevalence of hvKp, PLA due to *K. pneumoniae* has been steadily increasing. *K. pneumoniae* are divided into two types: cKP and hvKP.¹ Ckp is an

opportunistic pathogen which mainly infects immunodeficient patients or the immunocompromised population. HvKP can infect young healthy people without underlying diseases.² Increased virulence of hvkp is related to its hypermucoviscous phenotype and stronger ability of iron acquisition.^{3,4} HvKP often causes primary liver abscess and metastatic infections like endophthalmitis, meningitis, and so on.⁵ HvKP infections are more common in the Asian Pacific but now are occurring globally.

Here we report one case who presented in China with PLA and EE due to a relatively rarely reported serotype of hvKP. Different from previous reports, the ST of this strain was K64-ST1764 instead of the commonest ST11. It is especially noteworthy that antimicrobial susceptibility testing showed that this strain was sensitive to all antibiotics, which means it is not a KPC-Kp or a CRKP.

Case Presentation

An 80-year old Chinese male patient presented to the emergency department with nausea, vomiting, and epigastric discomfort for 2 weeks without treatment. This patient had a history of Type II diabetes mellitus, hypertension, and coronary heart disease. There was no relevant family history or history of genetic disease. Laboratory investigations revealed a white cell count 14.42×10^9 cells/L (normal range = $3.5\text{--}9.5 \times 10^9$ cells/L), 85% neutrophils (normal range = 40–75%), aspartate transaminase (AST) 10^9 U/L (normal range < 50 U/L), lactate dehydrogenase (LDH) 349 U/L (normal range = 109–245 U/L), random blood glucose 19.96 mmol/L (normal range = 3.8–6.2 mmol/L), blood urea 11.3 mmol/L (normal range = 2.1–8.6 mmol/L), creatinine $141.7 \mu\text{mol/L}$ (normal range = $35.2\text{--}97.5 \mu\text{mol/L}$). Severe infection and ketoacidosis were suspected so emergency doctors gave him antibiotics (imipenem combined with ornidazole), rabeprazole, antiemetic drug, and fluid infusion, but his condition worsened. Fever appeared and the highest armpit temperature was 39°C.

He was admitted to the Department of Gastroenterology for further treatment. Laboratory investigations revealed C-reactive protein 439.43 mg/L (normal range < 10 mg/L), serum sodium (Na) 133.9 mmol/L (normal range = 136–145 mmol/L), serum potassium (K) 3.71 mmol/L (normal range = 3.5–5.3 mmol/L), total bilirubin $21 \mu\text{mol/L}$ (normal range = 3.4–20.6 $\mu\text{mol/L}$), and alanine aminotransferase (ALT) 88.6 U/L (normal range < 50 U/L). Physical examination revealed mild epigastric tenderness. A right lobe liver abscess was identified on CT scan (Figure 1). Abdominal

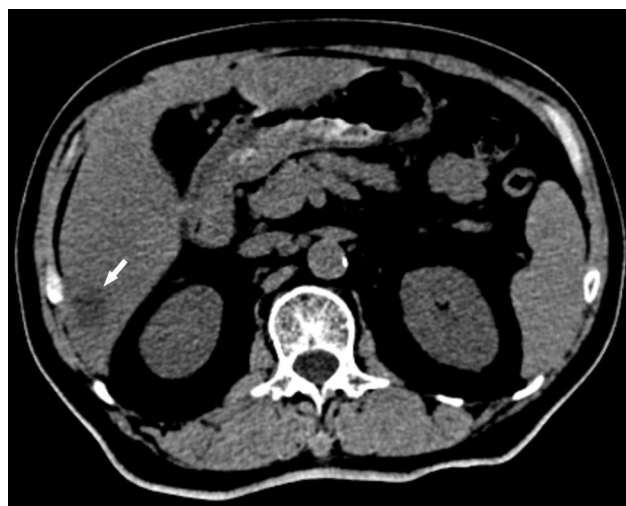


Figure 1 Abdominal CT scan showed a right lobe liver abscess (rounded, low density areas).

ultrasound showed a right lobe liver abscess (mixed echoes) with the size of 3.5×2.7 cm in the right liver lobe (Figure 2).

The patient was treated by anti-infection treatment (biapenem and morinidazole by intravenous injection), liver protection (polyene phosphatidylcholine), decreasing blood sugar, controlling blood pressure, and fluid infusion. Ultrasonography guided puncture aspiration for hepatic abscess was proposed but he refused. Both his white cell count and C-reactive protein were dropped after treatment but he was still feverish. Bacteria culturing and antimicrobial susceptibility testing were performed by using the VITEK-II Compact automated microbiological system and confirmed by using the broth microdilution method. Blood cultures, from both aerobic and anaerobic bottles, showed *K. pneumoniae* which was sensitive to all antibiotics.

The vision of this patient became blurred so urgent ophthalmologic consultation was performed. A B-scan ocular ultrasound was done and he was diagnosed as EE with bad prognosis. Intravitreal injection (vancomycin and cefoperazone) of eyes and eye drops were given. Finally, after obtaining the patient's consent, ultrasonography guided puncture aspiration was performed, which resulted in lowering the temperature and improving the inflammatory marker levels. Liver aspirate culture was also positive for *K. pneumoniae* and sensitive to all antibiotics (Table 1). The patient's eyes were swollen and empyema and the light perception of both eyes was basically lost. The ophthalmologist performed evisceration and drainage of the right eye, as well as repeated

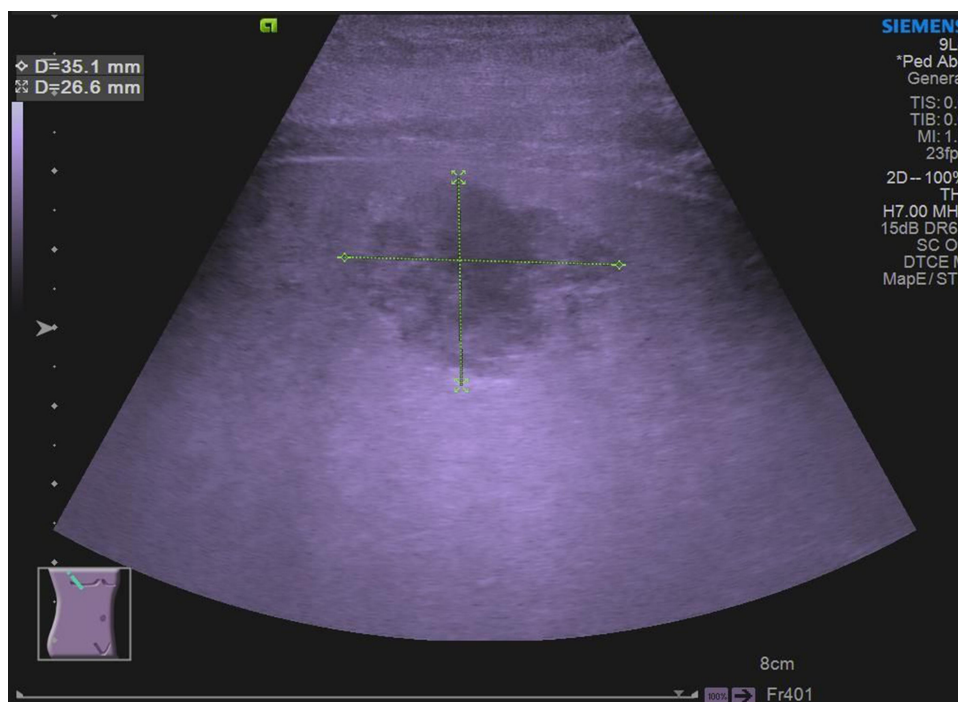


Figure 2 Abdominal ultrasound showed a right lobe liver abscess (mixed echoes, with a size of 3.5cm×2.7 cm).

intravitreal injection of the left eye. Abdominal ultrasonography was performed 6 days after the first therapeutic puncture. The abscess cavity decreased conspicuously

Table I Antimicrobial Susceptibility Testing Results for *K. pneumoniae* Isolate, Using Reference Broth Microdilution According to Clinical and Laboratory Standards Institute (CLSI) Guidelines

| Antimicrobial Agent | Minimum Inhibitory Concentration (µg/mL) | Interpretation* |
|-------------------------|--|-----------------|
| Amikacin | ≤2 | S |
| Ampicillin | >32 | S |
| Aztreonam | ≤1 | S |
| Ceftriaxone | ≤1 | S |
| Ceftazidime | ≤1 | S |
| Cefepime | ≤1 | S |
| Ciprofloxacin | ≤0.25 | S |
| Gentamicin | ≤1 | S |
| Imipenem | ≤1 | S |
| Levofloxacin | ≤0.25 | S |
| Ertapenem | ≤0.5 | S |
| Piperacillin-Tazobactam | ≤4 | S |
| Tigecycline | 0.5 | S |

Notes: *Interpretative criteria were applied according to CLSI document M100 (Performance Standards for Antimicrobial Susceptibility Testing, 28th ed, 2018) except for tigecycline where criteria established by the US Food and Drug Administration were used.

Abbreviations: R, resistant; S, susceptible.

and the second percutaneous needle aspiration was given. After treatment, the patient's eye swelling and the empyema was significantly improved and he became afebrile. He was given ceftriaxon 2 g by intravenous injection once a day for 4 weeks. Repeated blood cultures were negative and ultrasound reexamination showed the abscess cavity had disappeared. He was discharged and referred to the gastroenterology clinic for follow-up. During 15 months follow-up, the result was satisfactory.

Isolates were retested by 16S rRNA gene sequences as previously reported⁶ and *K. pneumoniae* was identified and reconfirmed.

String test was performed as previously reported.² The colony was grown at 37°C overnight on a sheep blood agar plate and then stretched by a bacteriology inoculation loop. A positive result is defined as the formation of a string >5 mm in length. Cultures of the blood, the aspirated pus from the liver abscess, and the contents of the eyeball all yielded *K. pneumoniae* with a positive string test (Figure 3).

Capsular serotype of each isolate was performed by polymerase chain reaction (PCR) as previously reported.⁷ PCR analysis indicated that the capsular serotype of the isolated *K. pneumoniae* was K64, which was validated by wzi sequencing as described.⁸



Figure 3 All cultures yielded *K. pneumoniae* with a positive string test (>5mm in string length).

MLST was performed by PCR amplification as previously reported⁹ and this strain belongs to ST1764.

Multiple biomarkers, including *peg-344* (+), *iroB* (+), *iucA* (+), *p_rmpA* (+), *p_rmpA2* (+), *c_rmpA* (-), *ureA* (+), *uge* (+), *wabG* (+), *allS* (+), *mrkD* (+), and *fimH* (+) were detected by PCR as described¹⁰ and multiple virulence genes were found in all the above isolates.

Screening for carbapenemase genes was performed by PCR as described¹¹ and *bla_{NDM-1}* and *bla_{KPC-2}* were not found in this K64 strain.

We evaluated the virulence of this *K. pneumoniae* strain in a *Galleria mellonella* infection model.¹² We infected the *Galleria mellonella* larvae with different concentrations (10^2 – 10^8 colony-forming units/mL) of *K. pneumoniae* and recorded the survival rate (Figure 4). This strain showed a strong concentration-dependent lethality to the larvae.

Discussion and Conclusions

The first clinical report about hvKp was in Taiwan in 1986.¹³ Although it is more common in the Asia-Pacific region, infections due to hvKp have gradually become global.^{14,15} Because hvKp was considered to have a hypermucoviscosity phenotype, the string test has been used to defining hvKP.³ However, more and more studies have shown that hypermucoviscosity is not pathognomonic for hvKp since this phenotype also can be observed in cKp strains.¹⁶ Recently, several virulence genes, like *iuc*, *peg-344*, *rmpA*, and *rmpA2*, have been shown to most accurately predict hvKp strains.¹⁶

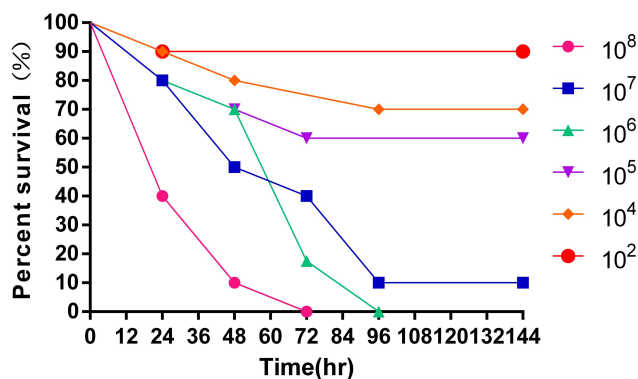


Figure 4 Survival curves for *Galleria mellonella* larvae inoculated with different concentrations (10^2 – 10^8 colony-forming units/mL) of the *K. pneumoniae* strain.

Since the 1980s, PLA due to *K. pneumoniae* has been steadily increasing. Especially in the Asia-Pacific region, hvKP has already become the predominant pathogen of PLA.^{17–19} Furthermore, these infections are occurring globally. A study in China has reported that among all PLA cases, *K pneumoniae* was the most common pathogen and a higher incidence of diabetes mellitus was shown in patients with *K. pneumoniae*-induced PLA.²⁰ Another study has reported that most of the liver abscesses were caused by *K. pneumoniae* and mostly occurred in patients with diabetes mellitus.²¹ The major clinical features of KP-PLA are fever, nausea, vomiting, abdominal discomfort, and laboratory inspection shows elevated white blood cell count and liver dysfunction. In this patient, all the above features can be found.

There are mainly three treatment methods: appropriate early antibiotic treatment, ultrasonography guided puncture aspiration or draining treatment, and open surgical drainage or surgical resection of the liver abscesses. We initially treated the patient with carbapenems and Morinidazole. After the condition stabilized, the antibiotics were changed to ceftriaxone for another 4 weeks. Some studies have suggested that the majority of PLA cases require drainage.²² A report showed that antimicrobial therapy alone was effective for small abscesses, while percutaneous needle aspiration or draining should be chosen for larger abscesses.²³ A study reported that liver abscesses due to *K. pneumoniae* that were >5 cm were likely to have a delayed response to therapy.²⁴ In the present study, the liver abscess was <5 cm (35×27 mm) and this hvKP strain was sensitive to all antibiotics. Even so, early antimicrobial therapy alone was ineffective. Once aspiration was performed, clinical improvement was observed. This suggested that, even for small abscesses,

puncture or drainage should be performed as early as possible when the effect of drug therapy is unsatisfactory.

In recent years, the incidence of EE has gradually increased. Gram-positive bacteria and fungal organisms account for the majority of the cases in the developed world, whereas gram-negative organisms like *K. pneumoniae* are more common in the Asia-Pacific region.²⁵ Now it has become a frequent complication: approximately 5% of individuals with hvKp bacteremia ultimately develop EE.²⁶

EE is a common metastatic complication of *K. pneumoniae* liver abscess.²⁷ Diabetes mellitus was considered to be a significant risk factor. The prognosis of EE is generally poor even with prompt diagnosis and aggressive treatment given. The final visual outcome was only light perception or worse in 89% of patients with EE associated with *K. pneumoniae*-induced PLA.²⁷ Diabetes mellitus and poor initial visual acuity were associated with poor visual outcome.²⁸ Reports showed that the main prognostic factor in *Klebsiella* EE is the presence of hypopyon which can be found in our patient.²⁹ This patient lost his eyesight.

It has long been recognized that almost all patients with severe infection with liver abscess and extrahepatic infections are infected exclusively with *K. pneumoniae* serotypes K1 or K2.² However, it is clear now that non-K1/K2 hvKp strains can express virulence genes and are capable of causing liver abscess and metastatic spread.^{16,30} The serotype of the isolated *K. pneumoniae* strain in our patient was K64, a relatively rarely reported serotype. This serotype has always been considered a cKP. But it is recently recognized that K64 is predicted to be observed for hvKp strains.^{31,32} Recent research finds that some cKp strains can acquire the hvKp virulence plasmid and evolve into hvKp strains.^{12,32} Our K64 *K. pneumoniae* strain showed strong virulence in the *Galleria mellonella* infection model. According to positive string test, the existence of multiple virulence genes, the strong lethality to the larvae and the severe invasive clinical manifestation of its infection, we can regard this K64 strain as a hvKp strain. Compared to the classification based on string test alone, our method is more reasonable.

In particular, ST was determined by MLST and the result was K64-ST1764 instead of the commonest ST11, which was considered to be predominant in Extended-Spectrum β -lactamases (ESBL)-producing strains and was prevalent in CRKP strains.^{33,34} However, previous reports showed that ST11 was predominant in K64 capsular type, hence K64 was considered as a prevalent type of CRKP.^{35–38} Furthermore, *bla*_{NDM-1} and *bla*_{KPC-2}, two important carbapenemase genes,

were not found in this K64 strain and antimicrobial susceptibility testing showed that it was sensitive to all antibiotics. Contrary to previous studies,^{31,32,36,39} these findings indicated that this K64 strain is not a KPC-Kp or a CRKP strain.

In conclusion, here we report one patient with PLA and EE due to a relatively rarely reported serotype of *K. pneumoniae*: K64. As the existence of multiple virulence genes, the strong lethality to the larvae and the severe invasive clinical manifestation and positive string test, this K64 *K. pneumoniae* can be regarded as a hvKp strain. Different from previous reports, the ST of this strain was K64-ST1764 instead of the commonest ST11. It is not a KPC-Kp or a CRKP, either. Further follow-up and research are required to investigate this strain.

Abbreviations

CRKP, carbapenem-resistant *K. pneumoniae*; cKP, classic *K. pneumoniae*; ESBL, extended-spectrum β -lactamases; hvKp, hypervirulent *K. pneumoniae*; KPC-Kp, *K. pneumoniae* carbapenemase (KPC)-producing; MLST, multilocus sequence typing; PLA, pyogenic liver abscess; ST, sequence type.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval

This case report was approved by the ethics committee of The Affiliated Wuxi Second People's Hospital of Nanjing Medical University.

Consent for Publication

Written informed consent for publication of his clinical details and clinical images was obtained from the patient.

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Author Contributions

Bo Zhao and Renjing Hu have contributed equally to this work and they are co-first authors. Conceived the study: Xiaoyun Wang, Bo Zhao; Acquired data, analyzed data: Bo Zhao, Renjing Hu; Performed the microbiological analysis: Renjing Hu; Wrote the manuscript: Bo Zhao; Contributed reagents/materials/analysis tools: Lei Gong,

Xiaoyun Wang; and Revised the manuscript: Xiaoyun Wang, Yingwei Zhu, Gaojue Wu.

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest to this work.

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