



Case report

Community-acquired liver abscess caused by capsular genotype K2-ST375 hypervirulent *Klebsiella pneumoniae* isolates



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ABSTRACT

Hypervirulent *Klebsiella pneumoniae* has been associated with community-acquired liver abscesses in relatively healthy subjects since the 1990s, occasionally accompanied by disseminated disease. While isolates of capsular genotype K1 belonging to sequence type (ST) 23 have been the most prominent causative pathogen of this syndrome, other virulent clones have been implicated sporadically in recent years.

A 68-year-old woman with diabetes in Okinawa, Japan suffered from a *K. pneumoniae* liver abscess, which recurred after a prolonged antibacterial treatment. The clinical course was further complicated with multiple sites of dissemination. Another 45-year-old woman living in Okinawa without underlying conditions was also diagnosed with a community-acquired *K. pneumoniae* liver abscess, which was cured with antibacterial treatment alone. Both of the causative isolates carried *rmpA* and aerobactin genes, and were confirmed as capsular genotype K2 and ST375.

K. pneumoniae K2-ST375 is a hypervirulent clone of epidemiological significance causing severe community-acquired infections in relatively healthy subjects. More information about clinical characteristics and molecular epidemiology of hypervirulent *K. pneumoniae* clones other than K1-ST23 should be accumulated.

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Introduction

Although *Klebsiella pneumoniae* had been recognized as an opportunistic pathogen that cause infections mainly in patients with underlying medical conditions [1], an increase in the cases of invasive community-acquired *K. pneumoniae* infections in relatively healthy persons was recognized in Taiwan in the 1990s [2]. While these patients typically presented with liver abscess that is sometimes complicated with disseminated endophthalmitis and meningitis, other types of infections such as necrotizing fasciitis and osteomyelitis have also been reported [2–4].

Detailed genetic analysis and molecular epidemiological studies of the representative isolates revealed that cases of community-acquired *K. pneumoniae* liver abscess in Taiwan were caused mainly by isolates of capsular genotype K1 [5]. While typical invasive infections caused by K1 isolates have predominantly been described from East Asian countries, similar clinical presentation due to K1 isolates has been reported among non-Asian persons from other areas of the world [6,7]. Most of the K1 isolates causing invasive infections have been classified into sequence type (ST) 23 by multi-locus sequence typing (MLST) and its close relatives [6,8].

Historically, isolates of genotype K2 have been recognized as the most common genotype among *K. pneumoniae* isolates causing urinary tract infection, pneumonia and bacteremia [1]. An epidemiological study analyzing *K. pneumoniae* isolates causing liver abscess in Taiwan and Singapore demonstrated that K2 was second most common genotype following K1 isolates [9]. K1 and K2 isolates collected in this study showed significantly higher resistance to phagocytosis by human neutrophils and higher

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lethality after inoculation to mice compared with other *K. pneumoniae* isolates. In contrast to K1 isolates, which uniformly belong to ST23, K2 isolates causing invasive infections have been classified into various STs [10,11]. K2 isolates causing severe infections have been reported in several STs, such as ST86 and ST380, but molecular epidemiology and clinical significance of hypervirulent isolates of capsular genotype K2 remains unclear thus far [12].

In this report, we describe two cases of community-acquired liver abscess caused by *K. pneumoniae* genotype K2 belonging to ST375 and carrying several virulence genes.

Case reports

Case 1

A 68-year-old woman with untreated diabetes mellitus was admitted to a secondary care hospital in Okinawa in Japan with a complaint of nausea and vomiting for one week in 2015. She had no travel history outside Japan. Her vital signs were as follows: blood pressure 90/69 mmHg, heart rate 102 beats per minute, respiratory rate 22 per minute, body temperature 37.5 °C, and SpO₂ 98% while breathing ambient air. Her physical exam was normal. Laboratory tests showed white blood cell count 13,880/ μ L, hemoglobin 13.3 g/dL, platelet count 105,000/ μ L, total bilirubin 1.3 mg/dL, aspartate transaminase 34 U/L, alanine aminotransferase 39 U/L, creatinine 0.60 mg/dL, and C-reactive protein 46.88 mg/dL, blood glucose level 394 mg/dL, and hemoglobin A1c 9.0%. Computed tomography (CT) scan of the abdomen revealed the presence of liver abscess across segments S4 to S8, measuring 5.2 cm \times 3.4 cm in size. Cefmetazole and metronidazole were administered empirically. A blood culture drawn on the day of admission grew *K. pneumoniae*. Antimicrobial susceptibility testing was performed with VITEK 2 (Sysmex bioMerieux Co. Ltd., Tokyo, Japan) automated system and the results were interpreted with Clinical and Laboratory Standards Institute criteria [13]. The strain was susceptible to cefazolin, cefmetazole, cefotaxime, cefepime, imipenem, gentamicin, and levofloxacin. Fever persisted on the sixth day of admission and bilateral multiple lung nodules and abscess in the right anterior cervical lymph node were documented by CT scan of the chest, despite being on an active agent cefmetazole. The antimicrobial treatment was changed to ampicillin-sulbactam.

On the seventh day, she recognized visual disturbance and conjunctival hyperemia that appeared in her right eye. A fundoscopic examination revealed the presence of subretinal abscess. A drainage tube was placed in the liver abscess and the culture of the abscess grew *K. pneumoniae* with antibacterial susceptibility patterns identical to those of the blood isolate. On the 42th day since initial presentation, CT scan of the abdomen demonstrated a decrease of the size of the liver abscess and the drainage tube was removed. Lung nodules and abscess in right anterior cervical lymph node also showed improvement. The treatment was changed to oral ciprofloxacin on the day 61, which was completed on the day 89. However, recurrence of the liver abscess in segment S8 measuring 2.7 cm \times 2.1 cm in size was documented by a follow-up CT scan on the day 130. The abscess was treated with intravenous ampicillin-sulbactam for 2 weeks then oral ciprofloxacin for 10 weeks without drainage. Resolution of the abscess was confirmed by another CT scan before the end of the antimicrobial treatment and the liver abscess did not recur thereafter.

Case 2

A 45-year-old woman with no significant medical history was admitted to the hospital at which the patient in case 1 had been treated, with a complaint of fever and shaking chills for two days in

2016. Her only significant travel history was to the Hawaiian Islands and Singapore ten years before. Her vital signs were as follows: blood pressure 108/60 mmHg, heart rate 126 beats per minute, respiratory rate 24 per minute, body temperature 39.7 °C, and SpO₂ 93% while breathing ambient air. Her physical exam was normal. Her laboratory tests showed white blood cell count 2,760/ μ L, hemoglobin 11.8 g/dL, platelet count 25,000/ μ L, total bilirubin 1.2 mg/dL, aspartate transaminase 87 U/L, alanine aminotransferase 66 U/L, creatinine 0.78 mg/dL, and C-reactive protein 10.93 mg/dL. Hypotension persisted despite intravenous fluid administration and her mental status worsened after arrival at the hospital.

She was transferred to the intensive care unit and cefmetazole was administered empirically. A blood culture drawn on the day of admission grew *K. pneumoniae*. The strain was susceptible to cefazolin, cefmetazole, cefotaxime, cefepime, imipenem, gentamicin, and levofloxacin. On the third hospital day, CT scan of the abdomen revealed the presence of liver abscess in segment S8 measuring 3.4 \times 3.0 cm in size. Percutaneous drainage of the abscess could not be performed due to the location of the abscess. The antibacterial treatment was changed from cefmetazole to cefotaxime for better central nervous system penetration, due to concerns over possible dissemination into central nervous system by a hypervirulent *K. pneumoniae*. The patient became afebrile in a few days and reduction of the size of liver abscess was demonstrated by a CT scan performed on the day 29 of admission. She was discharged from the hospital on the day 33 and treatment was continued with oral ciprofloxacin. The liver abscess did not recur after a total of 45 days of antibiotic treatment.

The colonies of the *K. pneumoniae* blood isolates from the two cases mentioned above were mucoid on agar plates and formed viscous strings of >5 mm in length when they were stretched with an inoculation loop. We performed capsular genotyping, MLST, and screening of *rmpA* and aerobactin genes of the isolates with the methods described previously [14]. Both isolates were capsular genotype K2, belonged to ST375, and carried *rmpA* and aerobactin genes.

Discussion

We present two cases of community-acquired liver abscess caused by K2-ST375 *K. pneumoniae* isolates carrying *rmpA* and aerobactin genes in patients without anatomical abnormality in the biliary tracts. The disease was complicated by multiple and protracted disseminated diseases in one of the two patients who had untreated diabetes.

The *rmpA* gene is frequently identified among hypervirulent *K. pneumoniae* isolates and is associated with enhanced capsule production, which is phenotypically recognized as hypermucoviscosity of the colonies on agar plates. In a study analyzing 151 bacteremic isolates of *K. pneumoniae* from Taiwan, carriage of *rmpA* was strongly associated with hypermucoviscosity of the colony [15]. In addition, isolates recovered from patients with abscess formation were more likely to have hypermucoviscosity phenotype.

Siderophores are small molecules utilized for acquisition of iron by bacteria in mammalian hosts. Aerobactin is one of the siderophores produced by *K. pneumoniae*, and its production by *K. pneumoniae* has been associated with invasive infections [16]. Gene disruption and complementation experiments using a hypervirulent *K. pneumoniae* isolate showed that, compared with other siderophores produced by the species, aerobactin had most significant impact on the bacterial growth in human ascites and serum as well as virulence in a mouse infection model [17].

The two *K. pneumoniae* K2-ST375 isolates recovered from our cases carried *rmpA* and aerobactin genes, and caused community-acquired invasive infections in a diabetic patient and an immunocompetent person. Although reports of invasive infections

caused by K2-ST375 isolates have been scarce thus far [10], our cases suggest that K2-ST375 isolates could be a hypervirulent clone of *K. pneumoniae* of epidemiological significance. ST375 was one of the major clones of hypervirulent *K. pneumoniae* of capsular genotype K2 at a hospital in China [18]. While a recent molecular epidemiological study of clinical isolates of *K. pneumoniae* in Japan identified no isolates belong to ST375 among 16 isolates of genotype K2, all K2 isolates were collected outside Okinawa, where the present cases occurred [14]. Okinawa is a remote island located between the main islands of Japan and Taiwan. It is therefore possible that Okinawa has unique molecular epidemiology of *K. pneumoniae* clinical isolates, as was observed in Taiwan, where K1-ST23 isolates were disproportionately abundant [19].

While K1-ST23 isolates have been widely recognized as the major hypervirulent clone of *K. pneumoniae* until recently, clinical and molecular analysis of global collections of blood isolates identified various hypervirulent isolates other than K1-ST23, and *rmpA* and aerobactin genes were good genetic markers to detect these isolates [11,20]. Accumulation of clinical outcome information of infections caused by various hypervirulent *K. pneumoniae* clones may inform management of this devastating clinical syndrome.

Consent for publication

Written consent to publish this case report was obtained from the patients and the copy of the consent is available for the journal on request.

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Authors' contributions

Kosuke Hoashi: Writing (Original draft preparation), Investigation (Clinical data).

Sohei Harada: Conceptualization, Writing (Review and editing).

Yoshikazu Ishii: Investigation (Molecular microbiological data).

Kotaro Aoki: Investigation (Molecular microbiological data).

Shin Ishikawa: Investigation (Clinical data).

Yusuke Oshiro: Investigation (Clinical data).

Takashi Shinzato: Investigation (Clinical data), Supervision.

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