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Case Report

Pyogenic liver abscess due to hypervirulent *Klebsiella pneumoniae* in a 14-year-old boy☆

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ABSTRACT

A 14-year-old otherwise healthy boy presented with right-sided back pain following high fever. Abdominal computed tomography scan showed a large liver abscess. *Klebsiella pneumoniae* (KP) was rapidly identified from peripheral blood using the melting temperature mapping (Tm) method, which enables identification of pathogenic microorganisms within four hours after patient sample collection. He was diagnosed with pyogenic liver abscess (PLA) caused by KP on the day of admission. The KP was the hypervirulent (hv) clinical variant (string test positive, serotype K1, sequence type 23, *rmpA* and *magA* positive). After intravenous antibiotic therapy and drainage of the abscess, his condition resolved. The highlights of this case report are a healthy child with hypervirulent *Klebsiella pneumoniae* liver abscess in Japan and the new Tm mapping method for rapid and accurate identification of the pathogenic microorganism.

1. Introduction

Klebsiella pneumoniae (KP) is a well-known Gram-negative bacterium that is often associated with community-acquired pneumonia. Although pyogenic liver abscess (PLA) rarely occurs in healthy children, it is associated with a high mortality rate without adequate treatment [1]. KP is one of the most frequent causes of pediatric PLA in Taiwan, and its hypervirulent variant (hvKP) has been reported as the cause of PLA in Southeast Asian countries [2,3]. These infections are characterized not only by severe PLA, but also by their invasive and metastatic spread. For patients with hvKP liver abscess, appropriate antibiotic therapy combined with percutaneous drainage of abscess improves clinical outcomes [4].

Rapid and accurate identification of pathogenic microorganisms is key in the management of such severe infectious diseases. In our hospital, we perform the novel "melting temperature (Tm) mapping method" to rapidly identify any microorganism that might be found in a clinical sample from sterile sites [5].

We herein report a case of hvKP infection in a 14-year-old boy with PLA. Early diagnosis was made and the causative microorganism was rapidly identified using the Tm mapping method, resulting in prompt antibiotic treatment.

2. Case report

A 14-year-old boy visited the emergency room of Saitama Children's Medical Center with a 3-day history of high fever and

Abbreviations: KP, *Klebsiella pneumoniae*; hv, hypervirulent; PLA, pyogenic liver abscess; Tm, melting temperature; CT, computed tomography; CRP, C-reactive protein; DNA, deoxyribonucleic acid; PCR, polymerase chain reaction; *magA*, mucoviscosity-associated gene A; *rmpA*, regulator of the mucoid phenotype A.

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cough. He had experienced right-sided back pain for 2 days. He had no gastrointestinal symptoms such as diarrhea, and had been previously healthy, with no medical history. None of his family members had any sign of infection. He was born and had lived in the Philippines, before moving to Japan with his family two years prior to this presentation. There was no history of contact with other visitors from the Philippines or any overseas travel. On physical examination, his vital signs were: blood pressure 124/87 mmHg, heart rate 142 beats per minute, body temperature 40.4 °C, and peripheral oxygen saturation 100% in room air. He had an agonizing look. There were no neurologic findings. The sclerae were not icteric and there was no neck stiffness. The lungs were clear, and no extra sound was heard on cardiac auscultation. The abdomen was soft, with no significant tenderness. He had tenderness in the right shoulder and back.

Peripheral blood analysis yielded the following results: white blood cell count, 25,200 cells/μL (neutrophils 85.4%, lymphocytes 1.9%); hemoglobin level, 14.6 g/dL; and platelet count 148,000 cells/μL. The C-reactive protein (CRP) level was 306 mg/L, and the serum creatinine level was 0.68 mg/dL. His serum aspartate aminotransferase and alanine aminotransferase levels were elevated (321 IU/L and 479 IU/L, respectively). His serum direct bilirubin and amylase levels were 0.2 mg/dL and 60 IU/L, respectively. A lumbar puncture was also performed in the emergency room. The cerebrospinal fluid (CSF) was clear, and the cell count was 6 cells/μL, glucose level was 77 mg/dL (serum glucose level 131 mg/dL), and protein level was 30 mg/dL. Chest X-ray upon admission revealed a large right pleural effusion without respiratory symptoms (Fig. 2). Abdominal ultrasonography and CT scan showed a right lobe liver abscess (Fig. 1A and B).

Two sets of blood cultures were obtained simultaneously upon admission. Tm mapping was performed on 1 mL of the peripheral blood sample. After isolation of deoxyribonucleic acid (DNA), we conducted a nested polymerase chain reaction (PCR), using seven universal bacterial primer sets. The data profile was analyzed using Roter-Gene® Q (QIAGEN GmbH, Hilden, Germany), and the Tm values were identified. The seven Tm values were mapped on two dimensions, and by comparing it to the database, KP was identified within 4 hours after blood collection (Supplemental figure 1). He was diagnosed with PLA caused by KP on the first day of admission. Intravenous ceftriaxone (4 g/day) and oral metronidazole (30 mg/kg/day) were administered (Table 1). On the 5th hospital day, KP was isolated from blood culture. The microorganism was sensitive to ceftriaxone, cefotaxime, aztreonam, and levofloxacin and resistant to ampicillin. Minimum inhibitory concentrations (MICs) for ceftriaxone, cefotaxime, aztreonam, levofloxacin and ampicillin were ≦1.0, ≦1.0, ≦4, ≦0.5 and 16 μg/ml, respectively (Supplemental figure 2). CSF culture was negative. The liver abscess did not resolve with medical treatment until hospital day 7, when it was percutaneously drained under ultrasound guidance using a pigtail catheter, which resulted in lowering the temperature, reducing right-sided back pain, and improving the inflammatory marker levels. Cultures of the drained pus, stool, and sputum also yielded KP with a positive string test. After admission, a chest X-ray showed a large amount of right pleural effusion without respiratory symptoms (Fig. 2). On hospital day 19, tube thoracostomy was performed and the pleural effusion was drained over 7 days. The pleural effusion was not purulent and yielded no bacteria on culture. Fluorescent antibody test showed negative results for *Entamoeba histolytica*. Ophthalmologic evaluation yielded normal findings without evidence of infectious endophthalmitis. The patient experienced neutropenia on hospital day 35, leading to a change from cefotaxime to aztreonam. On hospital day 49, aztreonam was changed to oral levofloxacin, 500 mg/day. We continued to treat him with antibiotics for 9 weeks. The percutaneous catheter was removed on hospital day 49. On hospital day 60,

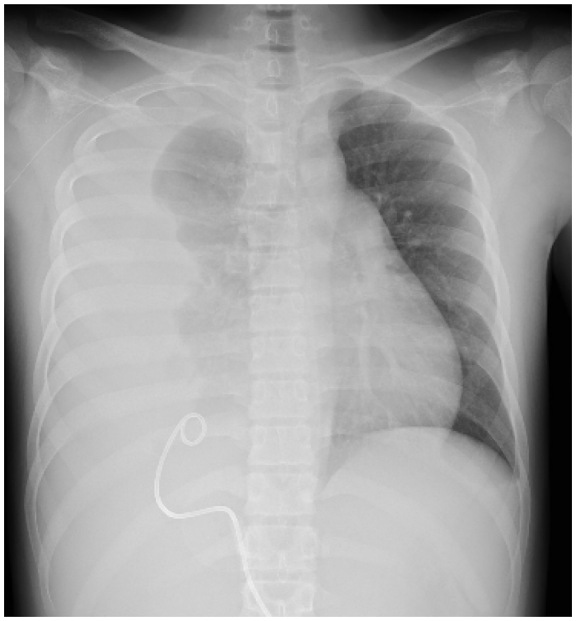


Fig. 2. Chest X-ray showing pleural effusion on the right side on hospital day 19.

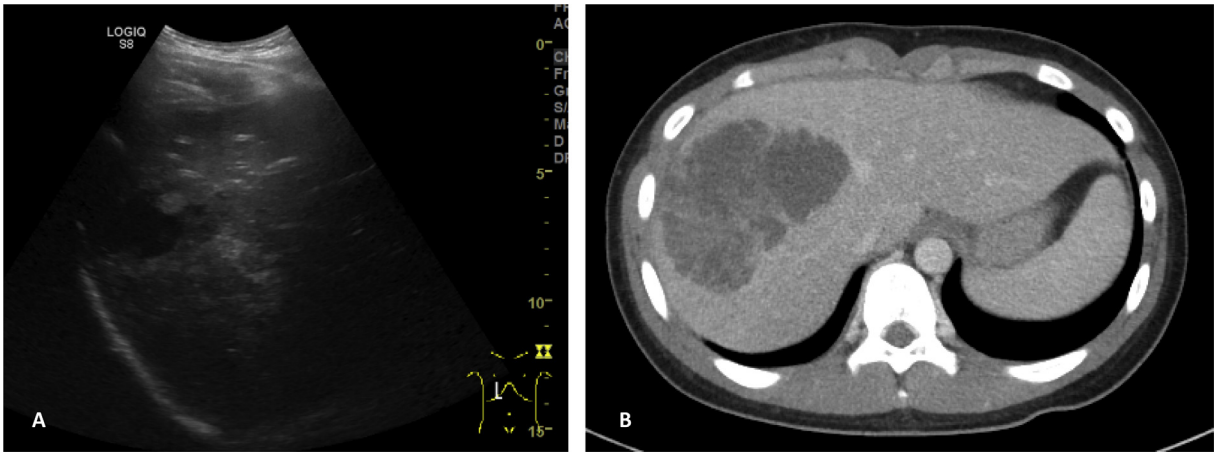
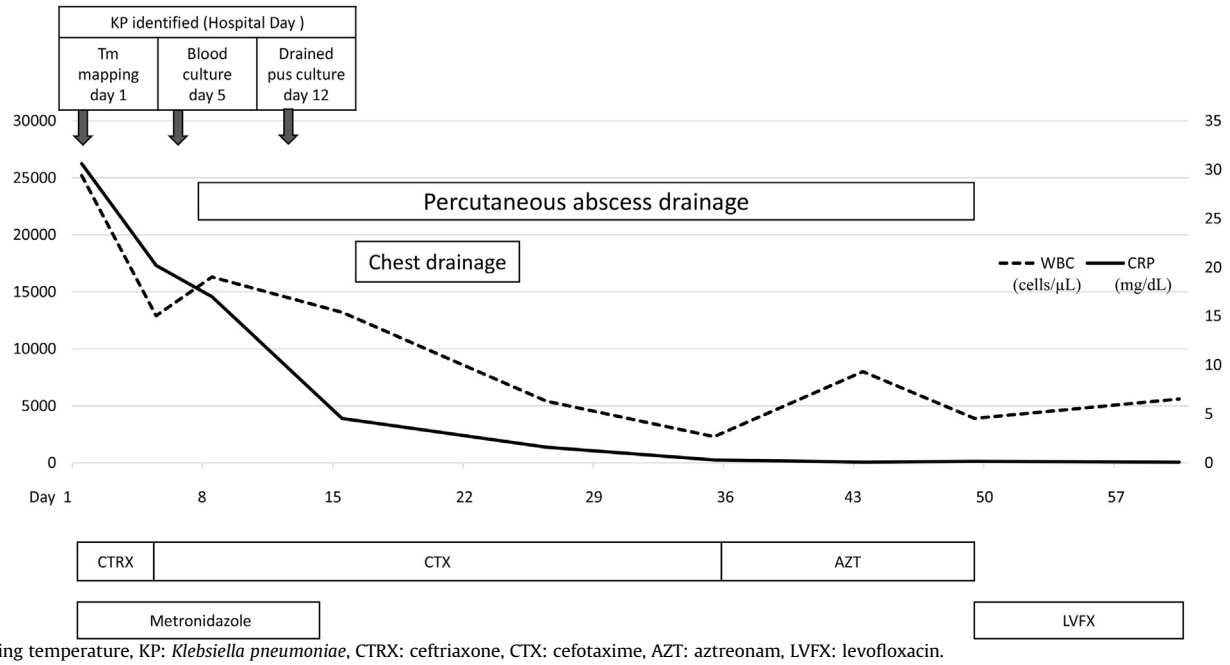


Fig. 1. (A) Ultrasonography showing a liver abscess. (B) Computed tomography scan showing a hepatic abscess.

Table 1
Clinical course of the patient.



Tm: melting temperature, KP: *Klebsiella pneumoniae*, CTRX: ceftriaxone, CTX: cefotaxime, AZT: aztreonam, LVFX: levofloxacin.

abdominal CT scan showed that the liver abscess had diminished in size. The patient's condition improved and was discharged.

The capsular serotype was K1, and multilocus sequence typing identified sequence type 23. These isolates were positive for the *rmpA* and *mega* genes on PCR.

3. Discussion

PLA rarely affects healthy children, especially in developed countries. Although mortality rates have declined with the use of combined antibiotic therapy and drainage, PLA results in severe complications [1,2,6]. Our PLA case demonstrated some typical features with a high fever, right-sided back pain and cough. Hsu et al. described that fever and abdominal pain were present in most PLA patients, and about one-third of patients presented with right upper abdominal pain and cough [2]. In this case, blood tests showed leukocytosis and high CRP level. And serum liver enzyme levels were also increased, a right lobe liver abscess was identified on ultrasonography and CT scan. The most common causative organism for PLA is reportedly *Staphylococcus aureus* [6]. A study from Taiwan reported KP as the most common microorganism isolated in cases of PLA in children [2]. In the 1980s, hvKP was associated with severe cases of PLA that progressed to cause extra-abdominal infections such as endophthalmitis and meningitis in healthy patients in Southeast Asia [3]. Recent reports from the US have mainly reported this type of infection in immigrants from the Philippines [7], although there are other reports of hvKP liver abscess in patients who had no history of traveling to Asia [8,9], which is in line with the findings in our case of PLA in a Filipino 14-year-old healthy boy, with no recent visit to or from the Philippines. These reports suggest that hvkP infection could develop into a serious health problem worldwide.

The mechanisms for classic KP entry into extraintestinal sites is either via disruption of the bowel wall resulting in the entry of gastrointestinal tract colonizers into the peritoneal cavity, or by the aspiration of oropharyngeal colonizers into the respiratory tract [10]. However, the access mechanism for hvKP remains unclear. In this case, hvKP was isolated from the blood, the drained pus from the liver abscess, stool, and sputum. It is currently speculated that leakage of KP from a patient's intestinal mucosa into the portal circulation results in bacterial translocation to the liver, leading to liver abscesses and bacteremia [4].

The type of hvKP has generally been defined semi-quantitatively by a positive string test. The string test is positive when a needle is able to generate a viscous string >5 mm in length by stretching bacterial colonies on a culture plate [4]. The serotypes of capsular antigen (K-antigen, K1 and K2) have been regarded as important virulence factors for KP. Investigation of the population structure of KP, by multilocus sequence typing, has revealed a clonal structure in the PLA-associated hypervirulent capsular serotype K1 isolates that belongs to sequence type 23 [4,11]. The *magA* (mucoviscosity-associated gene A) and *rmpA* (regulator of the mucoid phenotype A) genes are reportedly associated with a virulence factor and a hypermucoviscous phenotype [11]. These are thought to be related to the ability of hvKP to form pyogenic liver abscesses. There are few reports of pediatric cases of PLA associated with hvKP, and it remains unclear how hvKP achieves metastatic spread.

In the management of severe infectious conditions, it is important to detect the pathogenic microorganism and initiate effective antimicrobial therapy as soon as possible. In our case, we diagnosed the patient with PLA due to hvKP by the Tm mapping method using peripheral blood obtained on the day of admission. The Tm mapping method can rapidly identify more than 160 bacterial species using only seven primer sets and without sequencing. The Tm mapping identification requires a measurement error of no more than 0.1 °C among PCR tubes within the same run. As long as an optimal instrument is used, the identification is not instrument-dependent. One weakness of this method is that if the sample contains similar numbers of two or more species of bacteria, this method cannot identify the bacterial isolate. In this case, it can only be concluded that bacteria are present. The Tm mapping reagent kit (Mitsui Chemical Inc. Tokyo, Japan) is now commercially available in Japan.

We initially treated the patient with ceftriaxone and metronidazole. In this case, KP was sensitive to all tested antibiotics, except for ampicillin. Treatment of these infections with third-generation cephalosporins is preferred, although there is some debate as to whether first-generation cephalosporins could be equally effective because of the inoculum effect of KP-induced abscesses rather than the antimicrobial sensitivity patterns [4]. Although most strains of hvKP are susceptible to antimicrobials other than ampicillin, some cases of hvKP infection are resistant to third-generation cephalosporins due to extended-spectrum beta-lactamase- and carbapenemase-producing strains [12,13]. Studies have suggested that 80–90% of PLA cases require drainage [6,14]. A report of liver abscesses in children concluded that conservative management was effective for small abscesses (<5 cm), and percutaneous drainage was the treatment of choice for larger abscesses (>5 cm) [14]. Also, some patients required open surgery, because drainage is not effective for multiloculated abscesses, thick-walled abscesses, and hypervirulent organisms [1]. Our patient required percutaneous drainage, with the pigtail catheter left in place for 6 weeks, and antibiotic therapy for 9 weeks. Parenteral antibiotics, including ceftriaxone and aztreonam, were administered for 7 weeks, followed by oral levofloxacin for 2 weeks.

Meningitis and endophthalmitis are the most common metastatic complications of PLA due to hvKP, and high mortality has been reported in patients with meningitis [15]. In this case, the patient did not have an empyema, but a pleural effusion after admission. Yoon et al. also described the case of a patient with PLA due to KP who had a pleural effusion [16]. The pleural effusion was suspected to result from fluid that accumulates in the pleural cavity as a result of increased vascular permeability due to inflammation [17].

In conclusion, we have described a pediatric case of PLA caused by hypervirulent KP that was rapidly diagnosed by the Tm mapping method. The abscess resolved with long-term antibiotic therapy and drainage. Due to early diagnosis and treatment, the patient did not experience serious complications. Clinicians should be aware of the worldwide spread of hvKP.

Declarations

The authors declare that funding was not obtained for the preparation of this manuscript.

Ethics approval and consent to participate

Written informed consent was obtained from both patients for the publication of this case report and the accompanying images.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jiac.2018.07.006.

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