Cryptogenic invasive *Klebsiella pneumoniae* liver abscess syndrome

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KEYWORDS

Pyogenic liver abscess; Bacterial meningitis; *Klebsiella pneumoniae*; Thrombocytopenia; Lung abscess; Bacteremia; Diabetes mellitus; Taiwan

Summary

Background: *Klebsiella pneumoniae*-associated liver abscesses have distinct clinical and epidemiologic features.

Methods: We report the unusual case of an American patient with a *K. pneumoniae*-associated liver abscess and septic spread to other organs. We additionally present a comprehensive review of *K. pneumoniae*-associated liver abscess syndromes in adults.

Results: We identified three distinct *K. pneumoniae* liver abscess syndromes: the polymicrobial liver abscess, the monomicrobial cryptogenic noninvasive liver abscess, and the monomicrobial cryptogenic invasive *K. pneumoniae*-associated liver abscess (CIKPLA) syndromes, with distinct clinical, epidemiologic and outcome features. CIKPLA syndrome typically affects diabetic patients, mainly in Southeast Asia, and is complicated by septic spread to other organs.

Conclusions: The community-acquired, monomicrobial, *K. pneumoniae*-associated liver abscess syndromes that typically occur in the USA are mainly noninvasive and affect Asian or Hispanic persons. However, this report provides an alert that CIKPLA syndrome can occur in North America, and physicians need to be aware of it.

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Introduction

*Klebsiella pneumoniae* is a common pathogen responsible for diverse nosocomial and community-acquired infections, and is the third most common pathogen (10%) found in cases of nosocomial bacteremia, after *Escherichia coli* (20%) and *Staphylococcus aureus* (16.5%).1 About 72%2 to 88%3 of *K. pneumoniae* nosocomial bacteremias are monomicrobial.

The proportion of community-acquired versus nosocomial *K. pneumoniae* infections has increased markedly during the past two decades. In the USA, 41% of all *K. pneumoniae* infections are now community-acquired;4,5 the incidence is even higher in Taiwan, where it has been reported to be as high as 68%.6,7 In contrast to the 55% mortality associated
with nosocomial \textit{K. pneumoniae} bacteremia, the mortality rate with community-acquired \textit{K. pneumoniae} bacteremia varies between 14\% and 22\% (Table 1).

\textit{K. pneumoniae} is occasionally the cause of some liver abscesses. In the USA, liver abscesses are commonly polymicrobial,\textsuperscript{10} and \textit{K. pneumoniae} has been isolated in 7–27\% of cases. Interestingly, Rahimian et al.\textsuperscript{11} recently identified in New York a series of distinctive \textit{K. pneumoniae}-associated liver abscesses, which are mostly monomicrobial and uncomplicated. A distinct clinical syndrome of invasive monomicrobial \textit{K. pneumoniae}-associated liver abscesses frequently associated with complications such as meningitis, endophthalmitis, lung abscess, or fasciitis has been repeatedly reported. Endemic in Taiwan,\textsuperscript{12} mostly in patients with diabetes mellitus, this syndrome is anecdotally reported in western countries and almost never described in the USA (Table 1).

We present an unusual case of an American patient with \textit{K. pneumoniae}-associated cryptogenic liver abscess and bacterial meningitis. We also discuss the reported cases of the cryptogenic invasive \textit{K. pneumoniae} liver abscess (CIKPLA) syndrome, identifying its clinical and epidemiologic features.

\section*{Case report}

\subsection*{Patient symptoms and history}

A 42-year-old man of Filipino descent residing in Connecticut and working as a mechanic, who immigrated to the USA at age 22, reported to his primary care physician with a 4-day history of fever (40 °C (104 °F)), severe headache, malaise, and anorexia. His medical history was unremarkable, and negative for diabetes mellitus or corticosteroid treatment. The patient, his wife, and their children had just returned from a one-week vacation at a Rhode Island beach resort. The patient denied any recent travel to Southeast Asia, and did not recall any contact with anyone who had recently returned from that area. His last visit to the Philippines had been four years previously.

\subsection*{Evaluation and treatment}

A physical examination revealed lethargy, irritability, confusion, and neck stiffness. Results of an ophthalmologic exam were normal. Peripheral blood counts were unremarkable (leukocyte count = 8.7 × 10\(^9\)/L (88\% neutrophils and 8\% lymphocytes) and hemoglobin = 15.5 mg/dL), and results of liver function tests were within normal limits. He had mild hyponatremia (Na\(^+\) = 130 mEq/L (normal, 135–147 mEq/L)) and severe thrombocytopenia (platelet count = 19 × 10\(^9\)/L) (Figure 1). Results of computed tomography (CT) of the head were unremarkable.

A lumbar puncture was performed in the emergency department, after which the patient was started on 2 g ceftriaxone given intravenously (IV). A subsequent analysis of the cerebrospinal fluid (CSF) revealed pleocytosis (leukocyte count = 1.7 × 10\(^3\)/\(\mu\)L (81\% segmented neutrophils, 6\% lymphocytes, and 13\% monocytes)), an elevated protein level (400 mg/dL (normal, 20–45 mg/dL)), and a decreased glucose level (0 mg/dL (normal, 50–80 mg/dL)); these findings were consistent with bacterial meningitis. Serum and CSF Lyme immunoglobulin G and M levels (Specialty Labs, Santa Monica, CA, USA) ruled out Lyme disease. Results of an initial Gram stain and microscopic examination of the CSF fluid were unremarkable; however, the culture grew \textit{K. pneumoniae} after 48 hours of incubation. Unfortunately, the isolated \textit{K. pneumoniae} was not analyzed further to determine whether or not it was serotype K1 or K2. The isolate was resistant to ampicillin but sensitive to gentamicin, levofloxacin and cephalexin (cefazolin, cefepime, ceftazidime, ceftriaxone). Results of an enzyme-linked immunosorbent assay for the human immunodeficiency virus were negative.

Despite being treated with high-dose ceftriaxone (2 g IV twice daily) for bacterial meningitis, the patient remained febrile. On hospital day 5, a repeat lumbar puncture showed increasing pleocytosis. Because of his persistent fever, magnetic resonance imaging (MRI) of the brain was performed on hospital day 7, and it revealed multiple small ring-enhancing lesions consistent with septic emboli (Figure 2). Transthoracic and transesophageal echocardiograms showed normal valve anatomy and no patency of the foramen ovale. CT of the chest revealed a nodule suggestive of an abscess (Figure 3).

The patient next developed right upper quadrant tenderness and an elevation of his liver enzyme levels (serum aspartate aminotransferase = 39 U/L, serum alanine aminotransferase = 74 U/L, serum alkaline phosphatase = 237 U/L, and total serum bilirubin = 1.0 mg/dL). CT of the abdomen revealed a 4 × 3.5-cm multicystic abscess in the right liver lobe (Figure 4). Aspiration of the liver abscess returned frankly purulent material that subsequently grew \textit{K. pneumoniae} with an identical antibiogram to that of the strain isolated from the CSF. Metronidazole, 500 mg IV three times daily, was added to the ceftriaxone regimen.

One week later, repeat MRI showed increasing edema of the brain lesions and apparent development of new lesions. Over the next two weeks, however, the patient’s fever abated, the liver and lung lesions decreased in size, and MRI showed gradual resolution of the brain lesions. On follow-up three years later, the patient maintains a full recovery without developing any new health problems.
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Bacteremia</th>
<th>Metastatic infection</th>
<th>Geographical cluster</th>
<th>Diabetes mellitus</th>
<th>Hepatobiliary or GI anomalies</th>
<th>Comments and notes</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>K. pneumoniae</strong> bacteremia</td>
<td>N/A</td>
<td>N/A</td>
<td>USA: mainly nosocomial (60%)</td>
<td>(2%)</td>
<td>(21%)</td>
<td>Associated malignancy: 53%</td>
<td>36–55%</td>
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<td>Taiwan: mainly community-acquired (60–70%)</td>
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<tr>
<td>Community-acquired &lt;br&gt;K. pneumoniae pneumonia</td>
<td>+/–</td>
<td>Unusual</td>
<td>Taiwan: 62%</td>
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<td>Frequent associated with alcohol intake in Taiwan and South Africa (++++)</td>
<td>65%b</td>
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<td>South Africa and Singapore: 15%</td>
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<td></td>
<td>Rarely associated with alcohol intake in USA (–)</td>
<td>55%b</td>
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<td>USA: 1%</td>
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<td>+</td>
<td>++</td>
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<tr>
<td>Community-acquired &lt;br&gt;K. pneumoniae meningitis</td>
<td>+/–</td>
<td>Unusual</td>
<td>Taiwan and Singapore: 18–33%</td>
<td>(49–65%)</td>
<td>–</td>
<td>Occasionally associated with liver cirrhosis or thalassemia</td>
<td>43–66%c</td>
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<td></td>
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<td>USA: 1.2%</td>
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<td></td>
<td>+</td>
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<td>Polymicrobial liver abscess</td>
<td>+</td>
<td>Rare</td>
<td>USA: 7–27% cases</td>
<td>(10–25%)</td>
<td>(95%)</td>
<td>Frequent relapse: 41% (++++)</td>
<td>31–41%</td>
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<tr>
<td>Cryptogenic noninvasive monomicrobial &lt;br&gt;K. pneumoniae liver abscess</td>
<td>+</td>
<td>Rare/absent</td>
<td>Taiwan: 82% cases</td>
<td>++</td>
<td>+++++</td>
<td>Mainly community-acquired</td>
<td>&lt;2.5%</td>
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<tr>
<td>Cryptogenic invasive monomicrobial &lt;br&gt;K. pneumoniae liver abscess (CIKPLA)</td>
<td>++++</td>
<td>Endophthalmitis (60%)</td>
<td>Western countries (only among Asian or Hispanic persons)</td>
<td>(15%)</td>
<td>(0.6%)</td>
<td>No relapse ESBL (+) strains are rare</td>
<td>11%</td>
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<td>Lung abscess (40%)</td>
<td>Taiwan (endemic)</td>
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<td>+</td>
<td>+/–</td>
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<td>Meningitis (25%)</td>
<td>Japan, Hong Kong, China, Singapore, India, Thailand, Trinidad (cases reported)</td>
<td>(70%)</td>
<td>–</td>
<td>Mainly community-acquired</td>
<td>+</td>
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<td></td>
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<td>Necrotizing fasciitis (4%)</td>
<td>Osteomyelitis, prostatitis, muscle abscess, septic arthritis (exceptionally)</td>
<td></td>
<td></td>
<td>ESBL (+) strains are rare</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: ESBL, extended spectrum beta-lactamase; GI, gastrointestinal.

Signaling: absent or anecdotal (–); very rare (+/–); rare (+); occasional (++); frequent (+++); very frequent (++++); almost always (+++++).

a With early adequate appropriate antibiotherapy (at least one cephalosporin), associated mortality is 38%, compared to 88% when delayed or inappropriate. Nosocomial K. pneumoniae is more frequently resistant to aminoglycosides, antipseudomonal penicillin, and all three generations of cephalosporins than community-acquired strains.

b Mortality in patients admitted to the intensive care units in France, USA, and Taiwan were 43%, 55%, and 63%, respectively.

c The highest mortality is in Taiwan.

d As reported in one series in New York by Rahimian et al.11

e In Western countries, many of these cases were reported in patients of Southeast Asian origin and/or after returning from Southeast Asia.
We postulated that our patient had a *K. pneumoniae*-associated cryptogenic liver abscess which, because of its large size (4–11 cm), was likely the original lesion, and that his *K. pneumoniae* bacteremia had seeded to his lungs, brain, and meninges.

**Discussion**

Nosocomial and community-acquired *K. pneumoniae* bacteremia typically complicates *K. pneumoniae* suppurative infections (e.g., pneumonia, urinary tract infection, intravenous catheter site infection, meningitis) or results from underlying gastrointestinal or hepatic disease with a subsequent hepatic abscess, which is usually polymicrobial. Cryptogenic *K. pneumoniae* liver abscesses can be monomicrobial, and self-limited (noninvasive) even when associated with bacteremia. Lately, an invasive type of *K. pneumoniae* monomicrobial cryptogenic liver abscess presenting with metastatic septic seeding has been described.¹²

**Cryptogenic noninvasive *K. pneumoniae*-associated liver abscess syndrome**

The noninvasive *K. pneumoniae*-associated liver abscess syndrome is a rare condition worldwide, with a peak incidence in Southeast Asia. It accounts for 17% of the patients with *K. pneumoniae*-associated bacteremias in Singapore.¹³ In the USA, Rahimian et al.¹¹ isolated *K. pneumoniae* from 41% of liver abscess syndromes in two major urban hospitals in New York. The microorganism was exclusively recovered from Asian and Hispanic patients. Interestingly, one of the hospitals in that review served mainly the Chinatown neighborhood. The *K. pneumoniae*-associated liver abscess syndrome was community-acquired in all cases and presented mainly as a monomicrobial abscess (in 78% of cases).¹¹ All cases involved isolated liver abscesses without the extrahepatic
bacterial meningitis, endophthalmitis, or fasciitis identified in the invasive syndrome described in Taiwanese patients. A similar *K. pneumoniae* liver abscess syndrome has been described in Mississippi, in the USA. 14

Unlike polymicrobial liver abscesses, where the infection commonly originates from the biliary tract or the lower intestine, the monomicrobial *K. pneumoniae*-associated liver abscess is not associated with an identifiable gastrointestinal or hepatobiliary anomaly. 10 Therefore, the liver abscesses caused by non-invasive *K. pneumoniae* infection in the USA are typically monomicrobial, community-acquired, rarely associated with diabetes mellitus, and usually uncomplicated by extrahepatic seeding, with a very good clinical outcome (Table 1).

**Cryptogenic invasive *K. pneumoniae*-associated liver abscess syndrome**

Cryptogenic invasive *K. pneumoniae*-associated liver abscess (CIKPLA) syndrome is also typically community-acquired 6 and unrelated to gastrointestinal or hepatobiliary anomalies (Table 1). Unlike the cryptogenic non-invasive liver abscess syndrome, CIKPLA is highly associated with distant septic seeding and is distinguished by its geographical distribution. It is almost exclusive to Taiwan, 15 where it has been endemic, although a few cases have also been described in China, Korea, Singapore, Japan, India, Thailand, Trinidad, and Jamaica. 16–20 *K. pneumoniae* is the leading cause of cryptogenic liver abscesses in Taiwan, where it has been isolated in 30% (in the 1980s) to 80% (in the 1990s) of pyogenic abscesses. 12,15,21

According to Ko et al., more than 900 cases of *K. pneumoniae*-associated liver abscess syndrome have been reported from Asian countries in the last decade; fewer than 23 cases were reported from regions outside Asia. 6 In Western countries, however, anecdotal cases have recently been reported: a few cases of cryptogenic invasive liver abscesses associated with diabetes mellitus and endophthalmitis have been described in Spain, 22–24 Belgium, 25 Ireland (where the patient was a Taiwanese seaman), 26 Italy, 27 and Australia. 28

Compared with the monomicrobial cryptogenic noninvasive *K. pneumoniae* liver abscess syndrome, CIKPLA is characterized by a 20-fold increased association with diabetes mellitus and is frequently complicated by metastatic infections. 5,14,15,18,21,29–31

Endophthalmitis is the most common (as many as 60% of cases) and serious septic lesion of this syndrome, 29,31,32–36 although lung abscesses (40%), meningitis (25%), 37 and necrotizing fasciitis (4%) 38–41 are also encountered frequently. Additionally, prostatitis, osteomyelitis, septic arthritis, septic epidural abscesses, and muscle abscesses have occasionally been reported. 31,42,43

Compared to the polymicrobial pyogenic liver abscess, CIKPLA has lower mortality (11.3% vs. 41%) and relapse rates (4.4% vs. 41%). 15

In the USA, pyogenic liver abscesses are often polymicrobial. 44–46 and *K. pneumoniae* accounts for 7–27% of the strains isolated. 45–47 To our knowledge, only one case fitting the criteria for CIKPLA syndrome has thus far been reported in the USA. The patient was an African American man who presented with a community-acquired, monomicrobial, *K. pneumoniae*-associated liver abscess with meningitis and endophthalmitis. 48 The reasons for the geographic differences in the incidence of CIKPLA syndrome are unknown, but hypotheses should address differences in socioeconomic factors, possible occupational exposures (e.g., food handling), 49 defects in host defenses caused by diabetes mellitus or alcoholism, and possibly differences in genetic and immunologic susceptibilities in different ethnic groups.

Distinctive bacterial virulence is a probable contributing factor since a major cluster of *K. pneumoniae* isolates with genetic similarities was identified in Taiwanese patients with invasive liver abscesses and septic metastases, 12 including infections occurring in siblings. 50 *K. pneumoniae* serotypes isolated in Taiwanese patients with CIKPLA had a high prevalence of capsular polysaccharide serotypes K1 and K2 and an increased resistance to phagocytosis and intracellular killing. 51 Resistance to phagocytosis and bacterial death in human serum observed in the invasive strains has been linked to the virulence gene *magA*, which encodes the outer membrane protein of a mucoviscous exopolsaccharide. 52

There is an emerging concern about Gram-negative rods producing extended-spectrum β-lactamases (ESBLs), which are resistant to all β-lactam antibiotics except cephamycins and carbapenems, to most aminoglycosides, to trimethoprim–sulfamethoxazole, and sometimes to the fluoroquinolones. 53 *K. pneumoniae* is the most common species to produce ESBLs, 54 particularly in nosocomial infections (30.8% vs. 3.5% in community-acquired infections). 6 In fact, the prevalence of ESBL-producing strains of *K. pneumoniae* varies between 18.5% 55 and 53% 56 in nosocomial infections. The highest rates of ESBL-producing *K. pneumoniae* are reported in Eastern Europe (approximately 50% of isolates) 55 and South America (45% of isolates), followed by the western Pacific region (25%), Europe (23%), the USA (8%), and Canada (5%). 56 Strains isolated from both invasive and noninvasive *K. pneumoniae* monomicrobial liver abscesses 31 are highly susceptible to antibiotics but commonly resistant only to ampicillin. 25 ESBL-producing *K. pneumoniae* is rarely isolated from the aspirates of monomicrobial liver abscesses (invasive or noninvasive) which are commonly community-acquired conditions (4.3%). 11 Therefore, the treatment of choice would be a third generation cephalosporin, preferably ceftriaxone, because it accumulates in the vitreous fluid and CSF at therapeutic concentrations. 57

CIKPLA syndrome has a relatively good outcome. Endophthalmitis, meningitis and thrombocytopenia are its most alarming findings. A retrospective study identified thrombocytopenia (platelets <150 × 10^9/L) to be a predictor of a poor prognosis because it is associated with a 3-fold increased mortality rate over patients with normal platelet counts (37% vs. 11%), 13 a finding that has been confirmed by a more recent prospective study. 4 One half to two thirds of patients with associated meningitis die of their disease. 58

Despite his initial thrombocytopenia and central nervous involvement, the patient described in the case report had an uneventful recovery. When seen two years after his initial treatment, the patient had not developed any hepatobiliary, gastrointestinal, or metabolic disease. To our knowledge, this is only the second case of CIKPLA syndrome to be reported in the USA. A case of CIKPLA syndrome has been reported in Canada, but it involved a sailor of Indian descent who had a cryptogenic *K. pneumoniae*-associated liver abscess and necrotizing fasciitis after returning from a trip to Singapore.
and South Africa. Interestingly, our patient was of Asian descent but not diabetic.

Conclusion

CIKPLA is a community-acquired, mostly monomicrobial, solitary liver lesion frequently associated with diabetes mellitus and classically complicated by one or more septic conditions (e.g., meningitis, endophthalmitis, lung abscess, or necrotizing fasciitis). This syndrome occurs almost exclusively in Asia, possibly due to a distinctive virulent strain, but which is not particularly resistant to antibiotics, and therefore it usually has a good outcome. Although it is endemic in Taiwan, it can occur in North America, as our report shows. Therefore, physicians should be aware of this insidious syndrome and should identify early signs of meningitis or endophthalmitis because timely management remains critical for a good outcome. Physicians should recognize the risks of endogenous endophthalmitis and meningitis in complication of pyogenic liver abscesses, especially in patients with diabetes mellitus and/or of Asian descent. Of concern are whether future similar cases in North America will remain sporadic or become endemic. The identification of the serotype of K. pneumoniae responsible for any new CIKPLA cases, the analysis for ESBL-production and identification of virulence factors in future isolates such as the magA gene are warranted.

Conflicts of interest: No conflict of interest to declare.

References