Community acquired *Klebsiella pneumoniae*, K1 serotype

Invasive liver abscess with bacteremia and endophthalmitis

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ABSTRACT

A community-acquired syndrome of cryptogenic invasive *Klebsiella pneumoniae* (K. pneumoniae) liver abscess (CIKPLA) has been emerging worldwide over the past 3 decades, particularly in Taiwan and Korea. It is caused by highly virulent hypermucoviscous, rmpA positive *K. pneumoniae* serotype K1. This condition occurs in predominantly diabetic persons with no underlying hepatobiliary disease. Metastatic infections of the brain, meninges, lungs, pleura, bones, soft tissues, and eyes are unique features of this syndrome. We report a laboratory-confirmed regulator of mucoid phenotype (rmp)A-positive, K1 serotype *K. pneumoniae* from Saudi Arabia in 2 diabetic native Saudis presenting with community acquired, invasive liver abscess complicated in one by endogenous endophthalmitis. Following medical and surgical treatment, both patients were cured from liver abscesses, however there was unilateral permanent visual loss in one patient.

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Invasive K1 Klebsiella liver abscess syndrome ... Enani & El-Khizzi

emerging syndrome in 2 diabetic native Saudi patients who did not have history of international travel, to raise the awareness of physicians practicing in the Kingdom of Saudi Arabia (KSA) towards the existence of such serious condition in our region.

**Case Report. Patient 1.** A 46-year-old Saudi man from the Central KSA region with uncontrolled diabetes mellitus, presented with fever, right upper quadrant abdominal pain, and jaundice for 3 days. He experienced decrease in vision of the right eye before hospitalization, which got worse on admission before the initiation of antibiotics. He had no history of international travel, or hospitalization over the past 3 years. On physical examination, his temperature was 39°C, he was jaundiced with hepatomegaly and right upper quadrant tenderness, but without palpable masses. The patient was not examined by ophthalmologist on admission. Initial ultrasound did not detect any abnormality or gallstones. Laboratory tests showed: white blood cells - 22 (normal range: 4-11x10^9/L); alanine aminotransferase - 89 (normal range: 3-35 U/L); aspartate aminotransferase - 56 (normal range: 3-35 U/L); bilirubin - 126 (normal range: 3-17 µmol/L); albumin - 21 (normal range: 35-50 g/L); and alkaline phosphatase - 296 (normal range: 30-150 U/L). Clinical evaluation on admission considered ascending cholangitis or viral hepatitis as differential diagnoses. Intravenous ceftriaxone 2 g once daily and metronidazole 500 mg 8 hourly were started. Computed tomography (CT) of the abdomen carried out on the second day of admission showed hypo-attenuated lesion in segment 8 of the liver compatible with liver abscess (Figure 1a and Figure 1b). Simultaneously, percutaneous catheter drainage of liver abscess revealed bloodstained fluid, the culture of which grew *K. pneumoniae* resistant to ampicillin, but otherwise fully sensitive strain. The catheter was removed after 5 days when no more drainage was obtained. On the third hospital day, blood culture grew *K. pneumoniae* with the same sensitivity pattern as that of the liver abscess.

Ophthalmologic evaluation of the right eye, 4 days following admission showed edematous eyelid with conjunctival chemosis, and a plaque on the surface of the lens. The vitreous was turbid with no fundus view. A diagnosis of endogenous endophthalmitis was established. The left eye was normal. Vitreal tap of 0.4 ml of turbid fluid was analyzed, which showed negative gram stain and culture. Intravitreal injection of vancomycin one mg/ 0.1 ml, ceftazidime 2.25 mg/ 0.1 ml, and dexamethasone 0.4 mg/0.1 ml together with topical vancomycin, cefazolin were administered daily for one week. On day 12, the patient underwent right lensectomy and pars plana vitrectomy, as there was no clinical response to antibiotics. Nine days following drainage, the fever persisted despite 10 days of intravenous antibiotics. Echocardiography was normal. Laparotomy and resection of segment 8 harboring the liver abscess was carried out to control the fever. The patient had complete recovery of the liver abscess after 2 weeks of ceftriaxone and metronidazole followed by 4

![Figure 1 - Abdomen CT image: A) axial section of the upper abdomen post intravenous (IV) contrast (porto-venous phase) shows multiple small hypodensities at segment VIII of the liver (multi-loculated abscess [black arrows]) with faint focal anterior rim enhancement (upper white arrow); B) coronal reformatted section through the liver post IV contrast (arterial phase) shows multiple hypodensities at segment VIII of the liver (white arrows) with focal rim enhancement seen at the lateral aspect of the lesion (black arrows).](image-url)
weeks oral ciprofloxacin 500 mg 12 hourly. Eight weeks following discharge, a CT of the liver and colonoscopy were normal. Unfortunately, the patient lost vision in the right eye, and required evisceration.

Patient 2. A 56-year-old Saudi man, resident from the Southern KSA region with long standing hypertension, diabetes complicated with nephropathy and gallstones presented to the emergency department with 4 days history of fever, rigors, and epigastric pain associated with profuse night sweats, poor appetite, and had lost 5 kilogram body weight. He had been unwell for one month with subjective fever and chills. He had no recent, or remote international travel or hospitalization. On clinical evaluation, he was febrile with positive Murphy’s sign. Acute cholecystitis was suspected and intravenous cefuroxime 1.5 g and metronidazole 500 mg 8 hourly each were initiated on admission. Laboratory findings revealed white blood cells of 13.7 (normal range: 4-11x10^9/L); alanine aminotransferase and bilirubin were normal; and alkaline phosphatase was 160 (normal range: 30-150 U/L). Abdominal ultrasound on admission only showed gallstones, and fatty liver. After infectious diseases evaluation for the persistent fever, a CT of the abdomen 2 days following hospitalization was requested to rule out liver abscess. Meanwhile, a report from the microbiology laboratory of positive blood culture for Gram negative rods was received. The isolate was subsequently identified as *K. pneumoniae* resistant to ampicillin, but pan sensitive otherwise. Cefuroxime was switched to ceftriaxone 2 g once daily and metronidazole 500 mg 8 hourly was continued. A CT of the abdomen revealed multiple

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**Figure 2** - Contrast-enhanced abdomen CT scan: A) axial section of the upper abdomen post intravenous (IV) contrast (porto-venous phase) shows 2 variable in size hypodense lesions at segment VII (lower black arrows), and VIII of the liver (upper black arrow) of the liver with intense thick rim enhancement. The bigger lesion (at segment VII) shows multiple small air bubbles (white arrows); B) post IV contrast (porto-venous phase) at the upper and lower renal hila level shows hypodense lesion at the most inferior margin of the liver (black arrows).

**Figure 3** - An image of A) *Klebsiella pneumoniae* (K1 serotype) colonies appear mucoid and sticky on agar plate (white arrows), B) positive string test (white arrow).
liver abscesses in right liver lobe (segments 7 and 8) with gas formation (Figure 2a & Figure 2b). Lower chest cuts showed bilateral pleural effusion with atelectasis of the right lung base. The endoscopic retrograde cholangiopancreatography (ERCP) did not reveal common bile duct stones. Percutaneous CT-guided catheter drainage of the abscess retrieved 10 ml of thick pus, from which K. pneumoniae was identified expressing the same sensitivity pattern as the blood isolate. Catheter was removed after 6 days when no more pus was coming out. Fever persisted despite antibiotics for 18 days. Echocardiogram showed no vegetation. On the third week of hospitalization, the patient underwent laparotomy with open drainage of abscesses in segments 7 and 8, which were adherent to hepatic flexure. Cholecystectomy was also carried out as the gallbladder was dilated with pericholecystic fluid. The resolution of fever and remarkable clinical improvement occurred postoperatively. The patient was discharged on oral ciprofloxacin 500 mg PO twice daily for 6 weeks. Follow up abdominal CT and colonoscopy, 3 months after discharge, were completely normal.

**Laboratory identification and susceptibility testing.**

The K. pneumoniae from blood culture and liver aspirate was identified using the API20E system (BioMeraux, MRC Etoile France). The isolates were sticky and mucoid on agar plate and had a positive string test (Figure 3a & Figure 3b). Antimicrobial susceptibility was carried out using Microscan Walkaway (Siemens Healthcare Diagnostics Ltd., UK). Antibiotic testing was carried out for the following: ampicillin; amoxicillin-clavulanate; cefuroxime; ceftriaxone; cefazidime; ceftazidime; gentamicin; amikacin; ciprofloxacin; imipenem; meropenem; piperacillin-tazobactam; and cotrimoxazole. The isolates were resistant to ampicillin only. The bacterial isolates from the 2 patients were sent to a reference lab in London, UK (Opportunistic Pathogens Section, Health Protection Agency) for further identification using the multiplex polymerase chain reaction (PCR), which includes serotype specific targets for capsular types K1, K2, K5, K54, and K57, which have been associated with pathogenicity or invasive disease. Two putative virulence factors rmpA and wcaG were also sought. Both isolates had capsular serotype K1 and positive for these 2 virulence factors.

**Discussion.**

The global epidemiology of community-acquired K. pneumoniae infections has been changing over the past 3 decades.1 The distinct syndrome (CIKPPLA) is considered a globally emerging infectious disease, and affects relatively well, middle aged persons predominantly of Asian origin. More recent case reports and series describing the emergence of this syndrome were published from North America,5 South Africa,6 and Europe7. However, the epidemiology of K. pneumoniae liver abscess in the Middle East is unidentified, probably due to under reporting.

Although there are uncertainties on the predisposing factors, diabetes mellitus seems to be strongly associated with this serious condition. In some studies, the prevalence of diabetes was as high as 78% among patients with cryptogenic K. pneumoniae liver abscess.4 A reported 13% of patients with this syndrome have septic metastatic ocular or CNS lesions,4 other metastatic complications including pulmonary emboli or abscesses, prostatic abscess, osteomyelitis, septic arthritis, or psoas abscess. Mortality rate from primary liver abscess with bacteremia varies from 2.8-10%, but meningitis is associated with a 40-50% mortality rate.6 Klebsiella pneumoniae with capsular serotype K1 proved to be highly virulent and resistant to phagocytosis compared to non-K1 serotypes in several studies.8 The invasiveness of K1 K. pneumoniae appears to correlate with hypermucoviscosity phenotype (positive string test).

Mucoid-associated gene (mag)A, has been identified in 2004 as the major virulence factor of K. pneumoniae,9 and the main pathogen of primary pyogenic liver abscess10. Another virulence gene, the regulator of mucoid phenotype (rmp)A, is a plasmid-mediated regulator of the extracapsular polysaccharide synthesis. Accordingly rmpA-carrying strains were associated with hyper mucoviscosity phenotype, as well as with the invasive clinical syndrome.11

Septic metastatic endophthalmitis is a rare but devastating disease, which occurs when bacteria cross the blood-ocular barrier, and multiply within the eye. The first published report in the Middle East was from the Southern region of KSA describing a diabetic patient of Arab origin with endogenous endophthalmitis caused by K. pneumoniae that was isolated from the vitreous humor in association with liver abscess.12 Another report of 2 cases of endophthalmitis was from Riyadh, KSA affecting Arabian patients with diabetes.13 In both reports however, the Klebsiella species was not further investigated to determine the capsular serotype or virulence genes. It is worth mentioning that we have observed a trend for the emergence of community-acquired, monomicrobial K. pneumoniae pyogenic liver abscess in our institution over the past 5 years (2005-2010). Six cases were detected, one each in 2005 and 2009, while the other 4 in 2010. However, we could not confirm the invasiveness of the isolates as they were not available in our laboratory for further study.

Our first patient presented with acute symptoms of fever, abdominal pain and jaundice with decreasing vision in one eye. Despite clinical diagnosis of
endogenous endophthalmitis, the vitreous humor did not grow *K. pneumoniae*. This is explained by prior antibiotics the patient was receiving before the procedure, which apparently impaired the growth of bacteria. In the second patient, the symptoms were sub-acute with subjective fever, and significant weight loss, however the acute worsening with high fever, and abdominal pain brought the patient to the emergency room. Unfortunately, abdominal ultrasound failed to detect the liver abscess in both patients. In our opinion, the presence of gallstones in the second patient did not impact the development of liver abscess, as there was no dilatation of the biliary tree, and no stones were extracted by ERCP. Both of our patients were diabetic with poor glycemic control. This is in support with most series reported in the literature.3,8,14 In both patient’s blood and liver aspirate, *K. pneumoniae* was grown and was fully sensitive to all antibiotics, except ampicillin. This susceptibility pattern is classical in almost all reported cases of CIKPLA syndrome. Typing by multiplex PCR revealed that the isolates belong to K1 serotype, that is, *magA* positive, and further genomic testing detected other virulence genes *rmpA*, and the fucose synthesis gene *wcaG*.

The fever persisted despite proper antibiotics and percutaneous aspiration of liver abscesses, which compares to other series, where 28.6% of 79 patients had fever beyond 7 days of hospitalization.15 This has lead to laparotomy and partial resection of liver in the first patient, and open drainage of the abscess in the other. Both patients had complete recovery with no recurrence after one-year of follow up. Unfortunately, the first patient lost vision in one eye probably due to delay in identification and management of endophthalmitis.

The present report shows that CIKPLA syndrome due to *K. pneumoniae*, serotype K1, is possibly an emerging disease in KSA. Despite 2 previous reports of similar syndrome from our region, this present case positively confirm the identification of the invasive K1 strain. Patients with community-acquired *K. pneumoniae* invasive bacteremia -of undetermined etiology- need to be thoroughly investigated, preferably by CT scan, to rule out the underlying liver abscess. Diagnostic workup for metastatic complication should be pursued to avoid catastrophic disabilities.

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**References**