**CASE REPORT**

**Antibiotic-resistant hypervirulent Klebsiella pneumoniae causing community-acquired liver abscess: an emerging disease**

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**Abstract**

We report a case of a patient with fatal community-acquired pyogenic liver abscess (CA-PLA) caused by multiple drug-resistant, hypervirulent, *Klebsiella pneumoniae* (mdrhvKP). HvKP causing PLA has been described in East and South East Asia and it is recognized as an emerging infection worldwide. The syndrome is characterized by cryptogenic liver abscess formation without a previous history of hepatobiliary or colonic disease and metastatic spread of infection via the bloodstream to distant sites, including lungs, central nervous system and other organ systems. Diabetes mellitus is a recognized risk factor. Most previously reported cases have involved antibiotic susceptible strains of hvKP although reports of bloodstream infections caused by resistant strains, including carbapenemase producers, are increasing. Our report highlights the need for awareness of this devastating infection in patients presenting with sepsis and liver abscess without underlying hepatobiliary or colonic disease.

**INTRODUCTION**

Community-acquired pyogenic liver abscess (CA-PLA) caused by hvKP with haematogenous metastatic infection of extrahepatic sites such as lungs and central nervous system has been described in East (E) and South East (SE) Asia and is recognized as an emerging infection worldwide.

We report a fatal case caused by a multiply antibiotic resistant strain of hvKP in a previously well man.

**CASE REPORT**

A 47-year-old man presented to the Emergency Department of a tertiary care hospital with a 4-week history of fever, fatigue, myalgia, abdominal pain and dry cough that had become worse in the week prior to admission.

He was Nigerian, living in the UK. He had last visited Nigeria 4 months earlier and had taken antimalarial prophylaxis. He had type 2 diabetes mellitus (DM) and hypertension but was otherwise well.

Investigations showed early organ impairment, with mild liver enzyme elevation, acute kidney injury, raised white cell count and C-reactive protein (Table 1). Although a chest radiograph performed at the same time appeared clear (Fig. 1), the patient’s presentation was ascribed to a lower respiratory tract infection and he was discharged with oral co-amoxiclav.

The following day, blood cultures were positive with Gram negative rods seen on microscopy.

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He was admitted and treated with ceftriaxone and gentamicin. He complained of breathlessness and pleuritic chest pain. D-dimer was positive. He underwent a CT pulmonary angiogram and contrast CT of abdomen and pelvis. Pulmonary embolism was excluded but there were multifocal changes in the right lung consistent with infection. A 6-cm liver abscess was seen in the right lobe (Figs. 2–4). The Gram negative rods were identified as KE, resistant to co-amoxiclav, ceftriaxone and piperacillin-tazobactam, but susceptible to gentamicin and meropenem. Extended spectrum beta-lactamase (ESBL) production was confirmed. Table 2 shows the microbiology results taken throughout the course of the patients stay. The patient was transferred to intensive care because of multi-organ failure secondary to sepsis with a serum lactate of 10 mmol/L. He was agitated and complaining of headache and was intubated and ventilated. Continuous veno-venous haemofiltration was initiated. A plain chest radiograph showed progressive right middle zone consolidation (Fig. 5). Antibiotics were switched briefly to piperacillin-tazobactam but then to meropenem.

Liver ultrasound showed that the collection was predominantly solid with a central gaseous component, not amenable to surgical or radiological drainage.

Table 1: Blood results taken throughout the duration of the patients stay

| Investigation performed | Date          | 23/11/17 | 24/11/17 | 25/11/17 | 26/11/17 | 27/11/17 |
|-------------------------|---------------|----------|----------|----------|----------|----------|
| CRP (≤ 5 mg/L)          |               | 72       | 407.5    | 378.3    | 418.6    |
| Na (135–145 mmol/L)     |               | 132      | 133      | 147      | 143      |
| K (3.5–5.0 mmol/L)      |               | 3.8      | 3.8      | 4.1      |          |
| Creat (45–120 umol/L)   |               | 104      | 103      | 94       | 74       |
| Urea (3.3–6.7 mmol/L)   |               | 4.7      | 7.8      | 7.4      | 5.9      |
| eGFR (ml/min)           |               | 66       | 67       | 75       | >90      |
| Bill (3–20 umol/L)      |               | 39       | 61       | 73       | 70       |
| ALK Phos (30–130 IU/L)  |               | 82       | 138      | 227      | 293      |
| AST (10–50 IU/L)        |               | 82       | 353      | 783      |          |
| HB (130 – 165 g/l)      |               | 141      | 139      | 114      | 111      |
| WCC (4–11 10⁹/L)        |               | 13.81    | 10.06    | 6.05     | 5.62     |
| Neutrophils (2.2–6.3 10⁹/L) |         | 12.25    | 9.00     | 4.63     | 4.33     |
| PLT (150–450 10⁹/L)     |               | 130      | 29       | 16       | 48       |
| INR (0.9–1.20 ratio)    |               | 1.14     | 2.21     | 1.71     | 1.69     |
| APTT ratio             |               | 1.06     | 1.42     | 1.17     | 1.16     |
| CEA (<5 ug/L)          |               | <2       |          |          |          |
| Ca199 (<37 kU/L)        |               | 5        |          |          |          |
| AFP (<7 kU/L)           |               | <2       |          |          |          |
| LDH (<240 IU/L)         |               | 576      |          |          |          |
| Total protein (60-80 g/L) |          | 51       |          |          |          |
| Nuclear antibodies      |               |          |          |          |          |
| Anti-gastric parietal cell antibodies |     |          |          |          |          |
| Liver Kidney Microsomal Antibodies |   |          |          |          |          |
| Anti-smooth muscle antibodies |       |          |          |          |          |
| MITO                    |               |          |          |          |          |
| Cardiolipin IgG (<10 GPL U/ml) |   | 3.1      |          |          |          |
| Cardiolipin IgM (<10 MPL U/ml) |         | 2.7      |          |          |          |
| Ferritin (20–300ug/L)   |               | 8191     |          |          |          |
| PSA (<2.5ug/L)          |               | 4.3      |          |          |          |
| Cholesterol (1.0–5.0 mmol/L) |          | 3.5      |          |          |          |
| Triglyceride (0.5–2.0 mmol/L) |         | 6.1      |          |          |          |
| ANCA                    |               |          |          |          |          |
| Complement C3 (0.75–1.65 g/L) |        | 0.34     |          |          |          |
| Complement C4 (0.16–0.54 g/L) |         | 0.07     |          |          |          |
| DS DNA Ab (<10 IU/ml)   |               | 3 (Negative) |          |          |          |
| Anti-GM AB (<7 U/ml)    |               | 2.2 (Negative) |          |          |          |

AFP - Alpha – Fetoprotein, ALK Phos - Alkaline Phosphatase, ANCA – Antineutrophil cytoplasmic antibodies, Anti-GBM Ab – Anti-glomerular basement membrane antibodies, APTT – Activated partial thromboplastin time ratio, AST – Aspartate transaminase, BDG – Beta d glucan, Bili – Bilirubin, Ca199 – Pancreatic tumour antigens CA19–9, Cardiolipin IgG - Cardiolipin immunoglobulin G, Cardiolipin IgM - Cardiolipin immunoglobulin M, CEA – Carcinoembryonic antigen, Complement C3 - Complement component 3, Complement C4 - Complement component 4, Creat - Creatinine, CRP - C-reactive protein, DS DNA Ab - Double Stranded DNA antibodies, eGFR - Estimated glomerular filtration rate, HB - Haemoglobin, HBA1c - Glycated haemoglobin, IgA - Immunoglobulin A, IgG - Immunoglobulin G, IgM - Immunoglobulin M, INR - International normalised ratio, K - Potassium, LDH - Lactate dehydrogenase, MITO - Anti-mitochondrial antibodies, Na - Sodium, PLT - Platelets, PSA - Prostate specific antigen, WCC - White cell count.
Table 2: Microbiology results taken throughout the course of the patient's stay

| Investigation Performed       | Date                      |
|-------------------------------|---------------------------|
|                               | 23 November 17 | 24 November 17 | 25 November 17 | 26 November 17 | 27 November 17 | 28 November 17 |
| Blood culture +ve for K.      | +ve for K.            | Co-amox – R    | Gent—S         | Mero—S         | +ve for K.       |
| pneumoniae                    | pneumoniae            |               |                |                | pneumoniae       |
| Co-amox – R                  | Cipro—S               | Taz – R        | Mero—S         |                  |                  |
| Gent—S                       |                         |                |                |                  |                  |
| Mero—S                       |                         |                |                |                  |                  |
| Blood culture                 | HIV Negative           | HIV Negative   | Blood culture  | Negative        |                 |
|                              |                          |                | Negative       | Negative        |                  |
|                              |                          |                | Hepatitis B    | Negative        | Positive         |
|                              |                          |                | Hepatitis C    | Negative        |                 |
|                              |                          |                | Hepatitis A    | Negative        |                 |
|                              |                          |                | Hepatitis B    | Negative        |                 |
|                              |                          |                | Hepatitis C    | Negative        |                 |
|                              | CMV                      | Negative       | EBV            | Negative        |                 |
|                              |                          |                | BDG (< 8 pg/ml) | Negative        |                 |
|                              | CMV (copies/ml)         | <10 copies     | EBV (copies/ml) | <10 copies      |                 |
|                              | Adenovirus (copies/ml)  | <10 copies     | Aspergillus ELA | Negative        |                 |
|                              |                         |                | MRSA screen    | Negative        |                 |
|                              |                         |                | HTLV 1         | Negative        |                 |
|                              |                         |                | HTLV 2         | Negative        |                 |
|                              |                         |                | Toxoplasma IgG | Negative        |                 |
|                              |                         |                | Treponemal Serology | Negative |                 |
|                              |                         |                | EBV VCA IgG (past exposure) | Positive |                 |
|                              |                         |                | CMV IgG        | Positive        |                 |
|                              | Candida Auris Screen    | Negative       | TB Sputum screen | Negative – acid fast bacilli not seen |
|                              | TB Sputum screen        | Negative       |                |                  |                  |

Over the next 48 hours, the patient continued to deteriorate with worsening multi-organ dysfunction. Investigations for other causes of synthetic liver dysfunction were negative (Table 1).

He was noted to have fixed dilated pupils. CT head showed generalized oedema and a CT venogram/post contrast CT showed progressive cerebellar herniation but no abscess. Venous thrombosis could not be excluded and there was debris within the right ventricle suggestive of infection (Figs. 6–9).

The patient was too unstable for head magnetic resonance imaging (MRI) or lumbar puncture and had a cardiac arrest. Echocardiography demonstrated global hypokinesia but no severe impairment or vegetations.

He failed to demonstrate brainstem reflexes over a 4-hour sedation hold. He had two further cardiac arrests. He could not be resuscitated from a fourth despite ongoing aggressive fluid and inotropic support and died in early on the fourth day of admission.

Reference Laboratory analysis of the isolate confirmed capsular type K2 and the presence of regulator of mucoid phenotype genes rmpA and rmpA2, associated with enhanced expression of capsular polysaccharide and the hypermucoviscous phenotype.
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Figure 1: Frontal Chest Radiograph (on presentation): The lungs are clear. No pleural effusion. Cardiomedistinal contour are unremarkable.

Figure 2: CT Abdomen (Portal Venous phase). Axial image (Figure 2) and Coronal (Figure 3): there is a 6 cm lobulated mass located in the right lobe of the liver with peripheral enhancement and areas of central necrosis (gas) consistent with abscess formation. The remainder of the liver was normal, in particular, no portal or hepatic vein thrombosis.

DISCUSSION

CA-PLA with metastatic infection caused by hvKP in previously well hosts has been described in the Asia-Pacific region for many years and is recognized as an emerging infection globally (1, 2). Extrahepatic infections reported include pneumonia, endophthalmitis and meningitis.

HvKP strains are typically capsular type K1 or K2. The polysaccharide capsule is antiphagocytic and confers serum resistance. Hypervirulence is strongly (but not exclusively) associated with the hypermucoviscous phenotype, expression of which is mediated by upregulation of capsular polysaccharide synthesis by regulator of mucoid phenotype genes rmpA and rmpA2 (3, 4).

HvKP strains have been significantly less likely than non-hvKP to be resistant to multiple antibiotics. Zhang et al. (5) found ESBL production in 12.6% of hvKP compared with 42% of ‘typical’ strains (P = < 0.001).

Multi drug-resistant, hypervirulent, *Klebsiella pneumoniae* (mdrhvKP) infections are increasingly reported. A single centre study of community and healthcare-associated KP bloodstream infections by Li et al. (6) found high rates of resistance to third generation cephalosporin and fluoroquinolones (~60%) in hvKP and carbapenemase production in 20%. A nonfatal case of CA-PLA caused by ESBL-producing hvKP without metastatic complications has been reported from Taiwan (7).

Outside E Asia mdrhvKP strains causing CA-PLA have not been seen. In case series where antimicrobial susceptibilities were reported, none of the community-acquired hvKP infections
(which included 12 PLA) were caused by antibiotic resistant strains (4, 8).

Putative risk factors for CA-PLA caused by hvKP from areas outside E Asia include DM, male gender and recent travel. It is unclear whether Asian ethnicity is an independent risk factor. Prevalence of faecal carriage of KP (including K1 and K2 strains) in healthy populations in E Asia is higher than in European populations. Dietary or environmental exposures that affect gut colonization and subsequent invasive infection with hvKP remain undefined (2, 4).

DM was significantly more common in patients with hvKP infections compared with those caused by ‘typical’ KP in China (5, 6). In CA-PLA caused by hvKP the prevalence of DM is 40–65% (2).

Male predominance has been more marked in cases reported outside E Asia, up to 88% (9). The role of recent travel and potential exposure to hvKP in the pathogenesis of CA-PLA remains unclear.

Mortality from hvKP CA-PLA is low (<10%) but almost all reported infections have been caused by antibiotic susceptible strains. Early administration of effective antibiotics is known to reduce mortality in sepsis.
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CONCLUSION

The potential for severe sepsis and metastatic infection caused by hvKP infection and the possibility of antimicrobial resistance should be considered early in patients presenting with CA-PLA. Further epidemiological studies are needed to elucidate risk factors for this infection.

CONFLICT OF INTEREST STATEMENT

No conflict of interest for any of the named authors.

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CONSENT STATEMENT AND ANY GUARANTOR INFORMATION

Verbal consent was obtained at the time from the wife and brother of the patient as a next of kin by S.R.V (Consultant in charge), the permission for publication of the case report was documented on the digital medical notes.