

## Cryptogenic invasive *Klebsiella pneumoniae* liver abscess syndrome (CIKPLA) in Western Australia?

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### CASE STUDY

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### ABSTRACT

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Virulent serotypes of *Klebsiella pneumoniae* are recognised to cause metastatic infections at various sites. Prevalence of this invasive syndrome has been observed worldwide with predominance in Asian series. However, reports in an Australian setting have been limited. We report two cases of fulminating community-acquired invasive *Klebsiella pneumoniae* liver abscess syndrome occurring in two Caucasian patients, from two different, distant suburbs in Western Australia with no known clinical comorbidities prior to the hospital presentation and no history of recent travel overseas. The interval between both admissions was 18 days, where only one patient survived.

#### Key Words

Interventional radiology, invasive liver abscess syndrome, *Klebsiella pneumoniae*

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#### Implications for Practice:

##### 1. What is known about this subject?

Prevalence of this invasive syndrome has been predominantly seen in Asian series particularly from Taiwan. Anecdotal reviews have been reported globally as well. Reports from an Australian setting have been described in the past, but these cases mainly involved individuals not

native to Australia.

##### 2. What new information is offered in this case study?

The case study presents several important points:

- 1) *Klebsiella pneumoniae* liver abscess has devastating metastatic potential, particularly endophthalmitis and meningitis.
- 2) Poor visual prognosis with high likelihood of blindness seems inevitable despite early and aggressive treatment.
- 3) The diagnosis of endophthalmitis requires a high index of suspicion as the symptoms are often subtle and may go unnoticed, typically by the attending surgeons managing the liver abscess.
- 4) High mortality rates are seen with individuals with invasive meningitis.
- 5) Serotyping of isolates provides invaluable information in determining overall patient outcome.

##### 3. What are the implications for research, policy, or practice?

Two important implications emerged from this case study:

- 1) A high index of suspicion is essential for early diagnosis of invasive *Klebsiella pneumoniae* liver abscess syndrome and prompt treatment delivery is needed to reduce mortality and morbidity, particularly when ocular or central nervous system complications are seen, and especially in diabetic patients.
- 2) Treatment recommendations include all patients with *Klebsiella pneumoniae* sepsis be referred for early ophthalmological screening and delivery of extended spectrum cephalosporin for specified duration as discussed.

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### Background

*Klebsiella pneumoniae* is a common pathogen accountable for various nosocomial and community-acquired infections. Virulent capsular serotypes of *Klebsiella pneumoniae* are recognised to cause destructive invasive metastatic infections at multiple sites.<sup>1,2</sup> Prevalence of this invasive syndrome has been observed predominantly in Asian series with more recent global emergence.<sup>3–5</sup> Reports from an

Australian setting have been limited and previous local reports mainly involved Australian residents who are of Asian descent with recent travel to or from their native countries.<sup>6,7</sup>

We describe two Caucasian patients from two different and distant Western Australian suburbs, who presented with fulminating invasive *Klebsiella pneumoniae* liver abscess syndrome, with both cases occurring within the same duration. Both individuals had no recent travel overseas. These case reports may be the first invasive *Klebsiella pneumoniae* liver abscess syndrome to be described in Western Australia involving individuals native to the region. This rare but devastating syndrome has a high mortality rate, particularly seen in individuals with invasive meningitis.<sup>1,5</sup> A high index of suspicion is essential to diagnose endophthalmitis as the symptoms are often subtle. Visual prognosis is often poor and blindness seems inevitable despite early treatment.

### Case details

#### Case 1

A 67-year-old Caucasian lady with no known comorbidities and who was not previously diagnosed with diabetes mellitus, presented with lethargy, confusion, and poor oral intake for four days. Examination findings included a Glasgow Coma Scale (GCS) of 11/15, hypotension (88/55 mmHg)—mean arterial pressure of 66mmHg, tachycardia (100 beats per minute) and pyrexia (39°C), with bilateral lung crepitus, hepatomegaly, neck stiffness, a swollen right lower limb, and a cloudy right eye. Investigations showed metabolic acidosis (pH 7.13, pO<sub>2</sub> 115mmHg, pCO<sub>2</sub> 53mmHg, bicarbonate 17mmol/L), hyperglycaemia (36.4mmol/L), thrombocytopenia (17x10<sup>9</sup>/L), renal impairment (urea 14.6mmol/L, creatinine 140umol/L, eGFR 33mL/min/1.73m<sup>2</sup>, sodium 144mmol/L, potassium 3.8mmol/L), and a raised C-reactive protein (CRP 206mg/L), but a normal total white blood cell count (6.8 x 10<sup>9</sup>/L). The patient was not anaemic and hematocrit count was 37 per cent. Marked glycosuria, proteinuria, and haematuria were also noted. The patient was not coagulopathic and mild liver function derangement was noted.

The chest X-ray (CXR) showed bilateral pneumonic infiltrates. Electro- and echocardiogram were unremarkable. The CT abdomen confirmed a 50 x 44 x 57mm segment VIII multi-septated abscess while the MRI head revealed multifocal intracerebral micro-abscesses and right uveoscleritis with likely orbital compartmental syndrome (Figure 1). The lower limb Doppler confirmed multiple right calf abscesses. The patient was treated for

hyperosmolar non-ketotic coma (HONK) and septic shock. The patient was intubated, resuscitated, and commenced on intravenous ceftriaxone 2g, meropenam 1g, gentamicin 240mg, and ionotropic support before being transferred to this tertiary hospital.

**Figure 1: Case 1 patient's MRI orbits T2 SPAIR (Spectral Adiabatic Inversion Recovery)**



*Axial image demonstrating abnormal enhancement, right orbital proptosis and panophthalmitis changes*

The liver abscess was aspirated while the calf abscesses were de-roofed and vacuum dressing applied. Right hypopyon, chemosis, and proptosis were profound ophthalmological findings. The right eye was tapped for intravitreal cefazolin and vancomycin administration. The right eye was eventually eviscerated after clinical deterioration despite the intravitreal antibiotics. The sputum, blood, liver aspirate, and vitreous fluid cultured *Klebsiella pneumoniae*, which was sensitive to cefazolin, gentamicin, ciprofloxacin, cotrimoxazole, ticarcillin plus clavulanate, and was resistant to amoxicillin. The cerebrospinal fluid (CSF), urine, and calf wound cultures were sterile. Moxifloxacin was added to the antibiotic regimen.

The patient's hospital stay was complicated by atrial fibrillation and amiodarone infusion was commenced. The patient completed eight weeks of intravenous ceftriaxone and continued oral moxifloxacin for another four weeks. While in hospital, blood sugar levels were controlled with regular insulin, which was continued after discharge. Eight weeks later, the calf wound underwent a flap reconstruction, a prosthetic right eye was fitted, and the patient was assessed for a hearing aid for right sensorineural hearing loss likely secondary to the cerebritis.

The follow-up CXR, MRI head, and CT abdomen showed interval improvement. The patient was successfully discharged home after rehabilitation with further satisfactory follow-up with her general practitioner by the end of one year.

## Case 2

A 44-year-old Caucasian man with no comorbidities and who was not previously diagnosed with diabetes mellitus presented to his general practitioner with complaints of nausea and vomiting for one week on a background of polyuria and polydipsia for the last three months, which he never sought treatment for. He was referred to a tertiary hospital with profound hyperglycaemia (>25mmol/L) and a clinically septic picture. On examination, the patient was hypertensive (190/100 mmHg)—mean arterial pressure of 130mmHg, tachycardic (120 beats per minute), afebrile, and tachypnoeic (30 breaths per minute). Apart from an enlarged liver, no other significant systemic examination findings were noted.

Other investigations included arterial blood gas of pH 7.48, pO<sub>2</sub> 100mmHg, pCO<sub>2</sub> 19mmHg, bicarbonate 14mmol/L, a raised CRP (307mg/L), and total white blood cell count (26.1 x 10<sup>9</sup>/L). Mild liver function derangement was also present. Renal function (urea 7.8mmol/L, creatinine 70umol/L, eGFR >60mL/min/1.73m<sup>2</sup>, sodium 134mmol/L, potassium 4.1mmol/L) and coagulation profile were normal. The patient was also not anaemic and hematocrit count was 41 per cent. Glycosuria in the absence of ketonuria was noted. The patient was treated as HONK. The patient's GCS rapidly deteriorated to 11/15 requiring intubation. Intravenous piperacillin plus tazobactem 4.5g, gentamicin 320mg, ceftriaxone 1g, and aciclovir 500mg were commenced prior to the patient being transferred to this tertiary hospital.

CXR revealed bilateral pulmonary pneumonic consolidations while the CT abdomen revealed a 70mm diameter segment V hepatic abscess, which was drained on the same day via percutaneous catheter. The blood, urine, liver aspirate, and turbid CSF cultured *Klebsiella pneumoniae*, which was sensitive to cefazolin, ceftriaxone, cefalexin, gentamicin, ciprofloxacin, norfloxacin, nitrofurantoin, cotrimoxazole, ticarcillin plus clavulanate, piperacillin plus tazobactem and similarly, resistant to amoxicillin. Meropenam 2g, ciprofloxacin 400mg, and metronidazole 500mg were further added to the antibiotic regimen. The patient displayed signs of neurological deterioration with pupillary dilation and loss of motor reflexes on the same day of admission. CT head revealed global cerebral and cerebellar ischaemia, which was confirmed as brain death by positron

emission tomography (PET). Death was pronounced three days later.

Both patients were from two different, distant suburbs in Western Australia and had no history of recent travel overseas. The interval between both admissions was 18 days. Other than the lady in Case 1 who had worked with refugees while volunteering with the Salvation Army, there were no other risk factors identified in both cases.

## Discussion

The emergence of *Klebsiella pneumoniae* as an important pathogen of liver abscess is now being recognised with virulent strains reported worldwide.<sup>3–5</sup> Extra-hepatic manifestations of *Klebsiella pneumoniae* include a distinct invasive syndrome, which has been identified in the past<sup>1</sup> and is known for its devastating metastatic potential to cause meningitis, endophthalmitis, lung abscess, and fasciitis.<sup>1,2</sup> Its pathogenic mechanism remains unclear.<sup>4</sup> Several plausible mechanisms have been suggested including inoculation of normal colonisers from the gastrointestinal tract due to disruption of host protective barriers, aspiration of oro-pharyngeal colonisers, direct biliary tree dissemination, and haematogenous spread.<sup>9</sup> Previous reports have been noted from Asian series mainly from Taiwan. Despite reports of sporadic cases, more anecdotal reviews have now been reported in Western series.<sup>1,2,4,7</sup>

Diabetes mellitus is recognised as an important comorbidity seen in most patients with pyogenic liver abscess. These individuals are particularly susceptible and predisposed to septic metastatic complications, notably endophthalmitis.<sup>2–5,8,10–12</sup>

The virulence and invasive potential of *Klebsiella pneumoniae* is seen in the K1 and K2 capsular strains associated with the hypermucoviscous phenotypes coded by the *rmpA* genes.<sup>5</sup> The novel *magA* gene is recognised as an important virulence gene causing primary liver abscess and septic metastatic complications.<sup>4</sup> This gene, when exhibited, increases serum and phagocytosis resistance.<sup>4,5,11</sup> *magA*-positive *Klebsiella pneumoniae* are exclusively seen in the K1 serotype<sup>1</sup> and are highly lethal in mice.<sup>4</sup> Fung et al.<sup>12</sup> identified that all of the metastatic septic complications were caused typically by serotype K1 or K2. Furthermore, they found that the most common serotype of *Klebsiella pneumoniae* isolated from diabetic patients was K1 followed by K2. Interestingly, only serotypes K1 and K2 were identified in patients with septic endophthalmitis, primarily the K1 strain. The invasive *Klebsiella pneumoniae* liver

abscess syndrome is generally community-acquired and presents mainly as a monomicrobial liver abscess.<sup>2,12</sup> Unfortunately, we were not able to obtain the capsular serotypes for both patients as they were not performed then and the samples have now been disposed. The *Klebsiella pneumoniae* colonies in both our cases were described as “muroid and translucent”, however, no string test was documented.

The prevalence of *Klebsiella pneumoniae* metastatic infection ranges between 3.5–20 per cent.<sup>5</sup> *Klebsiella pneumoniae* endophthalmitis is now recognised as the most common cause of bacterial endophthalmitis worldwide, despite being considered rare previously.<sup>3,8</sup> The appearance of ocular symptoms between 48–72 hours<sup>5,12</sup> after pyogenic liver abscess has been diagnosed suggests that septic endophthalmitis from the *Klebsiella pneumoniae* liver abscess occurs via haematogenous spread and could be a consequence of late drainage.<sup>12</sup> It is likely that those infections and complications had arisen by the time of presentation and were not preventable, regardless of the choice of antibiotics.<sup>5</sup>

Poor visual prognosis with high likelihood of blindness seems inevitable despite early and aggressive treatment for *Klebsiella pneumoniae* endophthalmitis.<sup>1,3,7,8,10,12</sup> This could be attributed to the delayed presentation and hence the delayed treatment. Also, the diagnosis of endophthalmitis requires a high index of suspicion as the symptoms are often subtle and may go unnoticed by the surgical team managing the liver abscess, as it is an uncommon phenomenon.<sup>7,8</sup> Poor visual prognostic factors have also been identified, including rapid onset of ocular symptoms, unilateral involvement, presence of hypopyon, and panophthalmitic involvement,<sup>3</sup> all of which was present in our Case 1 patient. Thrombocytopenia (platelets  $<150 \times 10^9/L$ ) is a predictor of a poor prognosis<sup>2</sup> and high mortality rates are seen in these patients and typically in those with meningitis.<sup>1,5</sup> Despite this, cryptogenic invasive *Klebsiella pneumoniae* liver abscess syndrome has been reported with good outcomes.<sup>2</sup> The mortality rates have been reported between 2.8–10.8 per cent.<sup>5</sup>

Extended spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* are rarely isolated from community-acquired conditions<sup>2</sup> as evident in both our patients' culture isolates, hence parenteral third-generation cephalosporins is the treatment of choice as it can attain rapid CSF and vitreal concentrations<sup>1–3,8,10</sup> while carbapenems are the drug of choice for ESBL-producing *Klebsiella pneumoniae*.<sup>1</sup> Duration of antibiotic therapy depends on patient response

to treatment, but generally varies between two to four weeks for solitary abscess and six weeks for multiple abscesses.<sup>1</sup> Early synchronous treatment with intravitreal antibiotics should be considered rather than systemic antibiotics alone.<sup>7</sup> Concurrent treatment of the liver abscess with percutaneous catheter drainage offers better protection against both metastatic infection and mortality.<sup>5</sup> Other reports have shown aggressive hepatic resection produced better outcomes than conventional percutaneous drainage for patients with Acute Physiology and Chronic Health Evaluation II (APACHE II) scores of 15 or more.<sup>1</sup>

## Conclusion

Our literature review has concluded that a high index of suspicion is required for early diagnosis of invasive *Klebsiella pneumoniae* liver abscess syndrome when a diabetic patient, especially of Asian descent, presents with ocular or central nervous system symptoms.<sup>2,3,8,10</sup> Recommendations include that all patients with ocular symptoms who are being treated for pyogenic liver abscess or with an established *Klebsiella pneumoniae* sepsis be referred for early ophthalmologic screening.<sup>3,7,8</sup> Screening for metastatic disease elsewhere should be based on clinical grounds. Both our cases involved Caucasians who had been newly diagnosed with uncontrolled diabetes mellitus. Univariate analysis of a retrospective review by Lee et al.<sup>5</sup> revealed that diabetic patients were more likely to have metastatic infection and were more likely to die during hospitalisation than non-diabetic patients, but this was statistically not significant in the multivariate analysis.

Apart from the female in Case 1 coming in contact with refugees while volunteering with the Salvation Army, both individuals had no recent travel overseas. It is understood that the concept of *Klebsiella pneumoniae* colonisation is a requisite for, but not necessarily leading to, infection. However, the time lag from acquisition to infection, if or when it develops, remains unknown.<sup>9</sup> It is difficult to establish the means of acquisition in both our cases. We feel that it is justifiable to consider travel and exposure to individuals from endemic areas as a definite risk factor. Furthermore, Lee et al.<sup>5</sup> identified that an APACHE II score  $\geq 20$ , acute respiratory failure, and shock are the greatest positive predictive factors for metastatic infection at any site; an APACHE II score  $\geq 16$ , evidence of metastatic infection, septic shock, acute respiratory failure requiring ventilation, and gas formation revealed on imaging were significant predictors of death. They also found pigtail catheter drainage protected against death. These findings to some degree can be seen in our cases with the older female in Case 1 having an APACHE II score of 21 and the

younger man in Case 2 with a score of 16, both in acute respiratory failure requiring high ventilator support, and in circulatory shock, had no gas formation reported on imaging. Furthermore, the deceased man had a catheter drain performed for the liver abscess, while the lady had a slightly smaller liver abscess aspirated and is having a satisfactory follow-up with her GP till date.

In view of these disparities, until clinical trials are conclusive, in addition to drainage of collections, third-generation cephalosporins should be delivered promptly to patients with recognised risk factors that predict metastatic complications occurrence.<sup>5</sup> Concurrent intravitreal antibiotic therapy should be considered early on if endophthalmitis is suspected.<sup>7</sup> Taking into consideration that the prevalence of this syndrome is now not only confined to the Asia Pacific region, identification of *Klebsiella pneumoniae* capsular serotypes and virulence factors in future isolates are now warranted.<sup>2</sup>

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## PEER REVIEW

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## CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

## PATIENT CONSENT

The authors, Dulku G and Tibballs J, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.