Klebsiella pneumoniae liver abscess with endophthalmitis in a diabetic man with gallstones

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SUMMARY

Invasive liver abscess syndrome (ILAS) is caused by *Klebsiella pneumoniae* and is typically seen in people from East Asia, often with diabetes and gallstones. ILAS includes metastatic sequelae of the infection, commonly to the eyes. The case described below occurred in a London hospital. The patient's abscess was diagnosed on CT and MRI and he developed endophthalmitis secondary to metastatic spread of the infection. He was treated with intravenous and intravitreal antibiotics and discharged with a plan for vitrectomy and cholecystectomy as an outpatient. We discuss the epidemiology, risk factors, pathogenesis, prognosis and management of this rare condition. There have been a number of recent reports of cases of this nature outside of Asia and we believe greater awareness is required. A high index of suspicion should be held for the potential development of metastases in patients of this demographic presenting with abscesses of this nature.

BACKGROUND

Invasive liver abscess syndrome (ILAS) was described in the 1980s,[1] but it was not until 2012 that it was defined as a distinct syndrome.[2] ILAS is typically seen in patients from East Asia with 40%–75% having diabetes mellitus[3–7] and a similar proportion with gallstones.[8 9]

Almost all severe cases of ILAS: bacteraemia, liver abscesses and extrahepatic infections, are caused by *Klebsiella pneumoniae* serotypes K1 or K2, but not all infections with K1 or K2 serotypes result in this syndrome.[2]

There is a significant morbidity and mortality associated with the condition. Overall 10.6% develop extrahepatic metastatic infection, and common complications include central nervous system involvement, necrotising fasciitis and endophthalmitis.[4 5 10] Ophthalmic complications are often severe, particularly in those with diabetes, with more than 85% of patients developing a severe visual deficit.[2 11]

ILAS is endemic in Taiwan,[10] and increasingly recognised across North America and Europe,[2 6 12–18] although we are aware of only a handful of cases from the UK.[13 14 19 20]

CASE PRESENTATION

A 57-year-old Vietnamese man presented to the emergency department of a South London hospital in March 2020 with a 3-day history of rigours, profuse sweating and right-sided abdominal pain. He had a background of a left hemisphere meningioma resection, Grave's disease and type 2 diabetes controlled with metformin and gliclazide. His most recent travel to Asia was in December 2014.

On examination, he was alert and orientated. Auscultation of the chest revealed good bilateral air entry with slight left basal crackles and normal heart sounds. His abdomen was soft but tender in the right upper quadrant and he was passing concentrated urine. His initial observations were; temperature 37.5°C, heart rate 126 bpm, blood pressure 125/79 mm Hg, saturations 97% on room air and respiratory rate 27 breaths per minute.

His initial blood results revealed a C reactive protein (CRP) of 242 mg/L and an estimated glomerular filtration rate of 47, assumed to be an acute kidney injury in the context of an acute inflammatory process. Full blood count showed a normal white cell count (WCC) of 4.4 $\times 10^9$/L and haemoglobin of 149 g/L. His liver function tests were; bilirubin 18 mg/dL, alkaline phosphatase 123 u/L and alanine aminotransferase 85 u/L while international normalised ratio was 1.3. His blood glucose was 20.9 mmol/L and glycated haemoglobin (HbA1c) was 51. At this point, the differential diagnoses included common general surgical pathology such as appendicitis, cholecystitis or another hepatobiliary infectious process, as well as malignancy.

Blood cultures taken on admission grew a gram-negative organism after 9 hours that was resistant to amoxicillin and, based on sensitivity results, he was commenced on intravenous piperacillin/tazobactam 4.5 g three times a day with the addition of gentamicin 5 mg/kg/day to cover for organisms with inducible beta-lactamase activity. *K. pneumoniae* was subsequently isolated from this blood culture while his urine cultured no organisms. The following day, a CT scan of his thorax, abdomen and pelvis with contrast revealed a hypoattenuating, hypoenhanced, inhomogeneous lesion in the parahilar region of the central part of the liver, measuring 6.3×5.2 cm (figure 1). A specialist gastrointestinal radiologist deemed it most likely that the lesion was an abscess although not amenable to drainage at this stage. By then, his WCC had risen to 14.9×10^9/L (with a neutrophilia of 13.7×10^9/L). With continued intravenous fluids and antibiotics, his inflammatory markers trended downwards and renal function normalised.

On the third day of admission, he had blurred vision in his right eye, with conjunctival injection and pain in response to light and movement. Ophthalmology findings were of visual acuity 6/24 in the right eye and 6/9 in the left eye; localised vitritis and active nasal retinitis were detected and endogenous endophthalmitis was diagnosed. Of note, diabetic retinopathy grading was not sufficient

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Figure 1 A CT abdomen and pelvis in the coronal plane, 2 days after presentation: There is the hypoattenuating-hypoenhanced lesion in the central part of the liver (parahilar region), measuring at least 6.3×5.2 cm, which shows inhomogeneity. There are a few, slightly prominent retroperitoneal lymph nodes but with no significant enlargement.

to produce visual impairment in either eye. The patient was commenced on flucytosine 200 mg/kg/daily four times a day and ketorolac 10 mg three times a day for pain.

One week later, his vitritis slightly increased with further deterioration of vision (3/60). Vitreous biopsy and intravitreal cefuroxime 2 mg/0.1 mL and vancomycin 1 mg/0.1 mL was given. At this point, the ketorolac was held and a week's course of dexamethasone drops 0.1% four times a day and ofloxacin drops 0.3% four times a day were commenced alongside cyclopentolate 1% two times a day for 10 days. His right eye improved and

Figure 2 Funduscopy of the right eye on day 22 postpresentation showing endophthalmitis after initial intravitreal antibiotic injections.

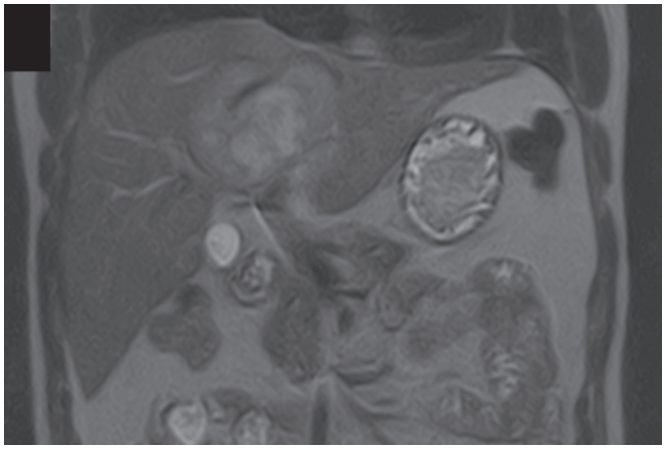

Figure 3 An MRI (T2 weighted, T2W) abdomen and pelvis in the coronal plane, 17 days after presentation: there is a complex multiloculate lesion with restricted diffusion within segments IV and VIII, measuring 7.8x 5.9 cm in diameter. There are calculi within the gallbladder with no biliary dilatation.

evidence of infection and inflammation in the vitreous decreased within a few days (figure 2).

Despite initial improvement, his WCC rose on day nine to 12.8 $\times 10^9$/L. MR cholangiography showed a complex multiloculated lesion within liver segments IV and VIII, measuring 7.8×5.9 cm in diameter (figure 3). It also revealed calculi within the gallbladder. A liver biopsy was not performed however a radiologically guided drain was inserted and the same organism was isolated from a pus sample.

OUTCOME AND FOLLOW-UP

On day 18, an ultrasound of his liver showed the abscess had resolved. At this point his WCC count was 6.2 $\times 10^9$/L and CRP was 6 mg/L. The patient was discharged 2 days later with a 5-day course of oral ciprofloxacin 500 mg two times a day, based on culture sensitivities and an abdominal drain in situ. A week later, he was reviewed as a surgical outpatient, the drain was removed and he was found to be making good progress. He has been booked for an elective laparoscopic cholecystectomy. The eye has continued to improve (figure 4), though at time of writing his visual acuity has not improved beyond 6/24 in the right eye, and the plan is to offer vitrectomy to clear the vitreous and hopefully improve the vision once the anterior chamber is completely free of inflammation.

DISCUSSION

Epidemiology and differential diagnoses

When first described over 30 years ago,[1] ILAS was exclusively seen in East Asia, and while it remains a rare condition in other continents, its prevalence is rising. Between 1992 and 2002, >900 cases of *K. pneumoniae* liver abscess were reported in Asia compared with 23 elsewhere, but in the following 10 years there were 38 cases described across two series in the USA alone.[2 12] Authors from Switzerland[18] and Ireland[6] have since published case series and our report adds to the growing number of those from the UK.[13 14 19 20]

Both imaging and culture techniques—to isolate the specific causative organisms—are used to delineate between malignant and infectious causes.[3] Ultrasound alone is used in nearly half of cases of pyogenic liver abscess[21] but in cases where the diagnosis is more difficult, MRI is regarded as the most sensitive imaging

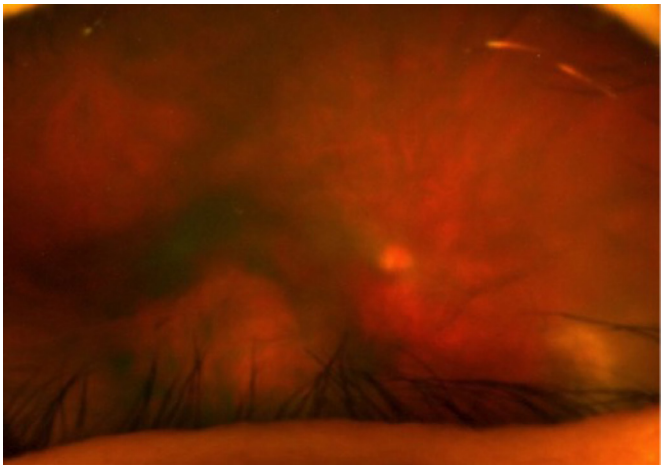

Figure 4 Funduscopy of the right eye on day 37 post-presentation showing ongoing endophthalmitis after further intravitreal antibiotic injections.

technique.[22] However, even MRI cannot differentiate between pyogenic and amoebic abscesses, highlighting the need for tissue sampling.[22] In addition, some infectious lesions, such as *Bacteroides fragilis* abscesses, can mimic malignant metastases.[23] Of the infectious causes of liver abscesses, two broad categories can be used[24]; those caused by bacteria (including amoeba) and parasites including hydatiform cysts and cystic echinococcosis and alveolar echinococcosis, both caused by helminths.[25]

Risk factors and virulence

Asian ethnicity appears to be a risk factor.[2 6] It has been theorised liver abscesses might occur when bacteria from the intestinal flora translocate across the intestinal epithelium into the portal system. Those of Asian descent have an increased prevalence of the virulent *K. pneumoniae* in faecal samples.[2 14 26] Specifically, capsular polysaccharide serotypes K1 and K2 and an increased resistance to phagocytosis and intracellular killing were seen in samples from Taiwanese subjects.[27] Host genetic factors may also play a role as two genes that convey resistance to Klebsiella (PHG1 and KIL1) have been identified.[28]

Patients with Klebsiella liver abscess are often diabetic[3 27–29] and it is a comorbidity in approximately 40%–75% of reported cases of ILAS.[4 6 7 10 12 13 15 30] The immunocompromise seen in diabetes is due to impairment of various components of the immune system. Specifically, patients with poorly controlled type 2 diabetes show impairment in the phagocytosis of both capsular serotypes and the chemotaxis of polymorphs.[31] Also, their leucocytes have reduced bactericidal effect due to impaired antioxidant systems.[30] Furthermore, increased blood glucose levels can be preferential for the replication of bacteria as well as weakening human immunity.[3 4 30] A study in mice models suggested that a diabetic phenotype provides a specialised environment that facilitates dissemination of Klebsiella from the gut into the circulation as described above.[32] As seen in this case, gallstone disease is also associated with biliary infections and subsequent pyogenic liver abscesses. Studies have shown this to be the case in over half on incidences and that it is associated with a more severe condition.[8 9 24 33]

Metastases

Metastases of infections are commonly seen with Klebsiella liver abscesses (8%–24%).[2 3] Specifically, meningitis, endophthalmitis, septic pulmonary emboli and empyema have been well-described plus rarer examples such as osteomyelitis, soft-tissue abscesses and necrotising fasciitis.[2] Cases of ILAS with septic metastasis have a 20-fold increased association with diabetes compared with non-invasive disease[15 30] and this comorbidity worsens the prognosis for this already life-threatening syndrome, leading to a higher rate of intensive care admission and mortality.[2 4]

Roughly half of cases of *K. pneumoniae* endophthalmitis originate from a liver abscess[13] and it is strongly associated with K1 and K2 serotypes.[34] Diabetes is the leading risk factor and it can be devastating for patients' vision with only 89% of patients left able to simply perceive light[11] and diabetes is also associated with a poorer outcome.[31]

Regarding potential mechanisms of metastasis, haematogenous seeding is a possibility[35] while direct spread into the chest via abscess rupture or through a hepatobronchial fistula has also been postulated.[36–38] Crucially, the harmful metastatic sequalae of ILAS can be difficult to pick up early as neither biochemical markers nor physical examination findings necessarily correlate. In fact, those with metastatic infections may be less likely to develop a fever or right upper quadrant pain and tenderness; perhaps a sign of a lesser immune response due to the likely presence of diabetes as a comorbidity.[38]

Prognosis and management

While rare in the western world, 1.0–2.3/100 000 population,[39] we believe ILAS is increasingly common, in part due to greater migration but also recognition of approximately equal incidences in both Asians and non-Asians outside Asia.[2] Furthermore, this syndrome carries significant risk of morbidity and mortality; the average hospital stay is 18.7±13.1 days with 24.9% requiring intensive care and approximately 5%–11% of cases result in death, compared with 2.5% in non-invasive cases of Klebsiella liver abscess.[2 4 15] Alarmingly, patients with metastatic infection often go longer before initiation of antibiotics.[38] It is, therefore, urgent that the cluster of infectious foci is recognised as a syndrome that must be treated promptly and aggressively with antibiotics, with good tissue penetration.[4] Cephalosporins and aminoglycosides make up the mainstay of treatment in Asia whereas in the USA, fluoroquinolones and metronidazole are often included,[2] however, it is crucial to base selection on in-vitro sensitivities.

Abscess drainage is also effective and resolution of the infection can be assessed with ultrasound, as described in this case.[2] Fortunately, extended spectrum beta lactamase producing *K. pneumoniae* are rarely seen in cases of this nature but the threat is increasing as antimicrobial resistance broadens.[2 15] Regarding endophthalmitis, early identification is key, and intravitreal sampling will guide appropriate intravitreal antibiotic regimen.[13] Finally, identification of ILAS may present an opportunity to pick up previously undiagnosed diabetes and good control of blood sugar levels in known patients with diabetes can prevent metastatic spread of infection.[2 30]

CONCLUSION

In conclusion, *K. pneumoniae* is an important cause of ILAS, a condition strongly associated with gallstones and diabetes, which has devastating effects elsewhere in the body, notably in the eye, via metastatic spread. There is growing evidence that this syndrome, once almost exclusive to East Asia is becoming more prevalent globally. Epidemiological studies are required to quantify this, meanwhile greater awareness of the condition, its

relation to diabetes and poor blood sugar control, and its effective management are warranted.

Learning points

- *Klebsiella pneumonia* liver abscesses can metastasise and cause invasive liver abscess syndrome.
- Invasive liver abscess syndrome (ILAS) is most prevalent in East Asians due to the make up of their gut commensals and genetics.
- ILAS is typically seen in diabetics due to the associated immunocompromise.
- Endophthalmitis is a common and important sequelae.
- Prompt treatment with highly penetrant antibiotics is required.

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