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Case Report

CASE REPORT

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

S. Rodriguez-Villar[1,*], A. Fife[2], C. Baldwin[1] and R. R. Warne[3]

[1]Critical Care Department, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK, [2]Microbiology Department, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK, [3]Department of Neuroradiology,King's College Hospital, London, SE5 9RS, United Kingdom

*Correspondence address. Critical Care Department, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK. Tel.: +44 (0) 203299 8226; E-mail: sancho.villar@nhs.net

Abstract

We report a case of a patient with fatal community-acquired pyogenic liver abscess (CA-PLA) caused by multi 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 diabetis 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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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
Bili (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 10^9/L)	13.81		10.06	6.05	5.62
Neutrophils (2.2–6.3 10^9/L)	12.25		9.00	4.63	4.33
PLT (150–450 10^9/L)	130		29	16	48
INR (0.9–1.20 ratio)	1.14		2.21	1.71	1.69
APTTR (0.85–1.15 ratio)	1.06		1.42	1.17	1.16
CEA (<5 ug/L)			<2		
Ca199 (<37 kU/L)			5		
AFP (<7 kIU/L)			<2		
LDH (<240 IU/L)			576		
HBA1c (4.1–6.0%)			9		
BDG (<8 pg/ml)				Negative	
IgG (6.34–18.11 g/L)				9.55	
IgM (0.53–2.23 g/L)				2.75	
IgA (0.87–4.12 g/L)				0.74	
Total protein (60-80 g/L)				51	
Nuclear antibodies				Negative	
Anti-gastric parietal cell antibodies				Negative	
Liver Kidney Microsomal Antibodies				Negative	
Anti-smooth muscle antibodies				Negative	
MITO				Negative	
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				Negative	
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-GBM 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, APTTR - 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.

He was admitted and treated with ceftriaxone and genta micin. 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 KP, 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 haemoflitration 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 2: Microbiology results taken throughout the course of the patients 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. pneumoniae* Co-amox – R Gent—S Mero—S					
Blood culture		+ve for K. pneumoniae Cipro—S Gent—S Mero—S				
HIV		Negative				
Mid-stream urine		Negative				
Sputum culture			+ve for K. pneumoniae Co-amox – R Taz – R Mero—S ESBL producing			
Resp. Viral screen			Negative			
HIV			Negative			
Blood culture			Negative			
Hepatitis B			Negative			
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 EIA				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

Aspergillus EIA - Aspergillus enzyme immunoassay, BDG - Beta D Glucan, Cipro - Ciprofloxacin, CMV - Cytomegalovirus, CMV IgG - Cytomegalovirus Immunoglobulin G, Co-amox - Co-amoxiclav, EBV - Epstein-Barr virus, EBV VCA IgG - Epstein-Barr Virus viral capsid antigen Immunoglobulin G, ESBL producing - Extended-spectrum beta-lactamase producing organism, Gent - Gentamicin, HIV - Human Immunodeficiency Virus, HTLV 1- Human T-lymphotropic virus 1, HTLV 2 - Human T-lymphotropic virus 2, Mero - Meropenem, MRSA - Methicillin-Resistant *Staphylococcus aureus*, R - Resistant, Resp. viral screen - Respiratory viral screen, S - Sensitive, Taz - Piperacillin + Tazobactam, TB sputum screen - Tuberculosis sputum screen, Toxoplasma IgG - Toxoplasma Immunoglobulin G.

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

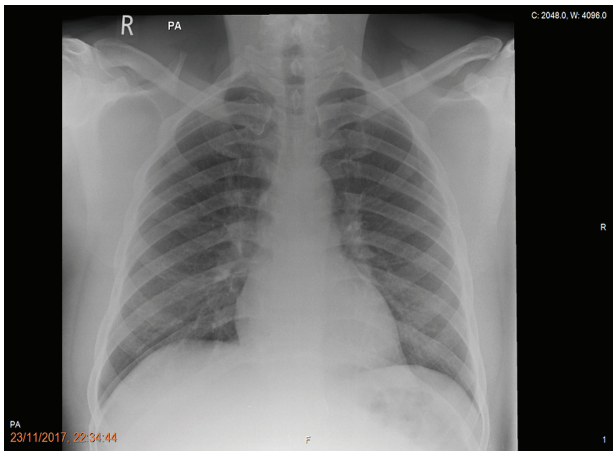

Figure 1: Frontal Chest Radiograph (on presentation): The lungs are clear. No pleural effusion. Cardiomediastinal contour are unremarkable.

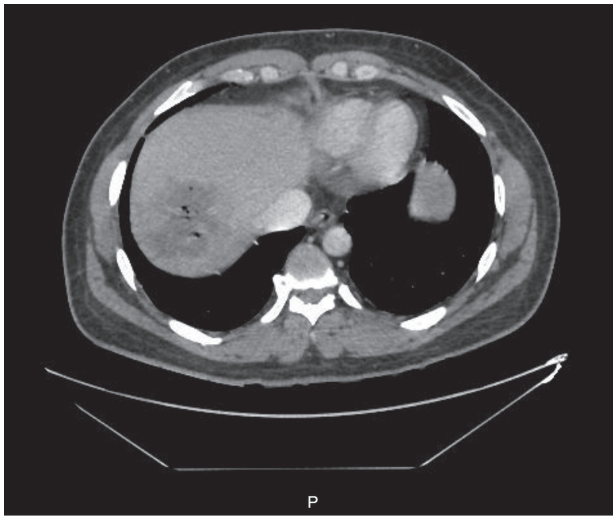

Figure 2: CT Abdomen (Portal Venous phase). Axial image (Figure 2) and Coronal (Figure 3): there is a 6 cm lobulated mass located in the right lobe of the liver with peripheral enhancement and areas of central necrosis (gas) consistent with abscess formation. The remainder of the liver was normal, in 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, endopthalmitis 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 ($P = < 0.001$).

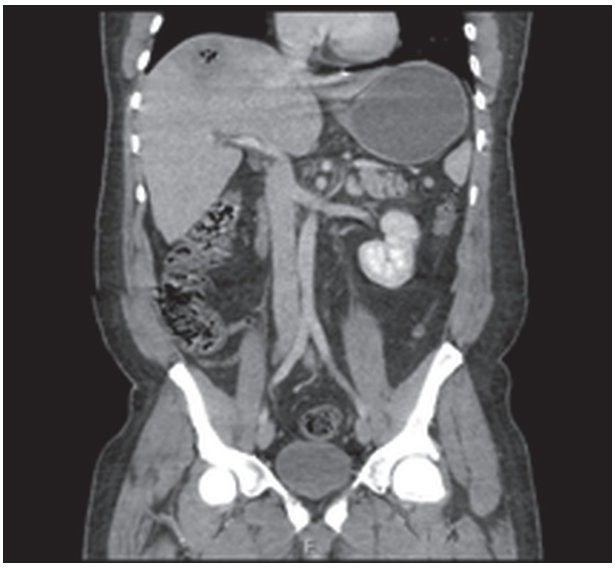

Figure 3: CT Abdomen (Portal Venous phase). Axial image (Figure 2) and Coronal (Figure 3): there is a 6 cm lobulated mass located in the right lobe of the liver with peripheral enhancement and areas of central necrosis (gas) consistent with abscess formation. The remainder of the liver was normal, in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

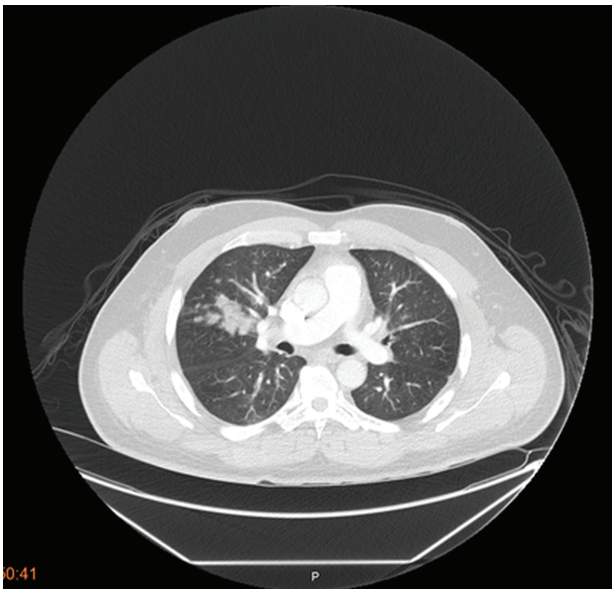

Figure 4: CT pulmonary angiogram. Axial image (lung windows): there is nodular right upper lobe air space opacification with surrounding ground glass nodules noted. No lung abscess demonstrated.

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

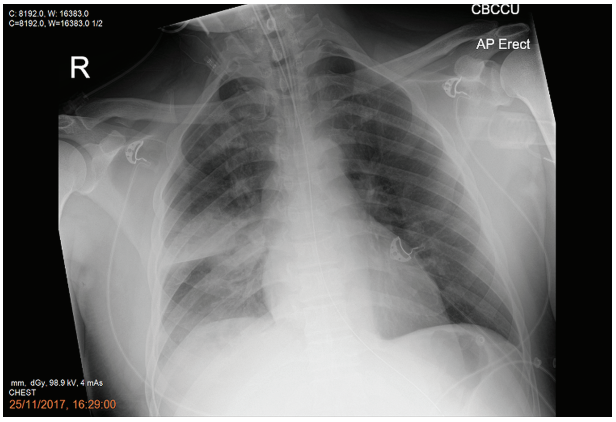

Figure 5: Frontal chest radiograph. Central lines and tubes appropriately sited. There is loss of volume of the right lung with elevation of the right hemidiaphragm and air space opacification of the lateral aspect of the right mid zone. Left lung is clear.

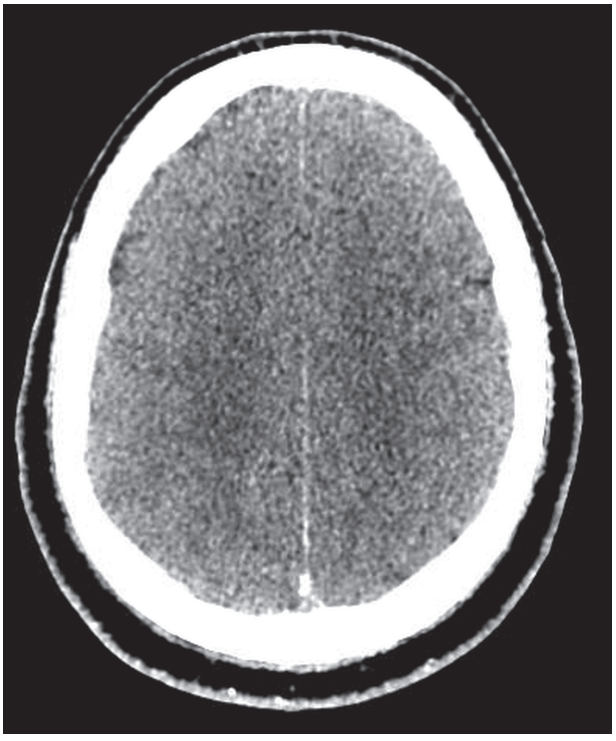

Figure 6: CT head (non-contrast). Axial image: There is cerebral sulcal effacement of both hemispheres at the convexity in keeping with cerebral oedema.

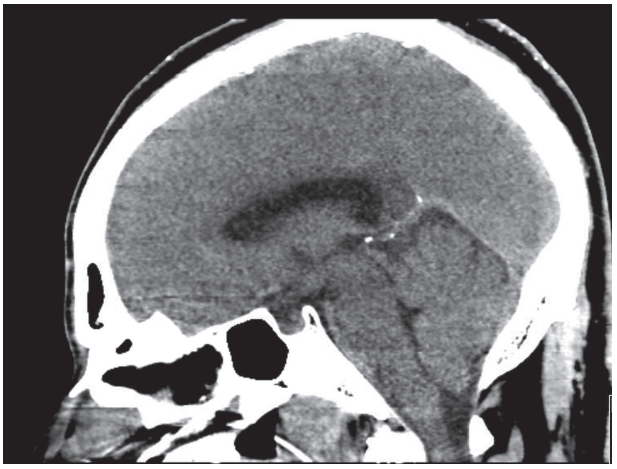

Figure 7: CT head (non-contrast). Sagittal Image: there is preservation of the suprasellar and pre pontine/pre medullary cisterns. The cerebellar tonsils are above foramen magnum.

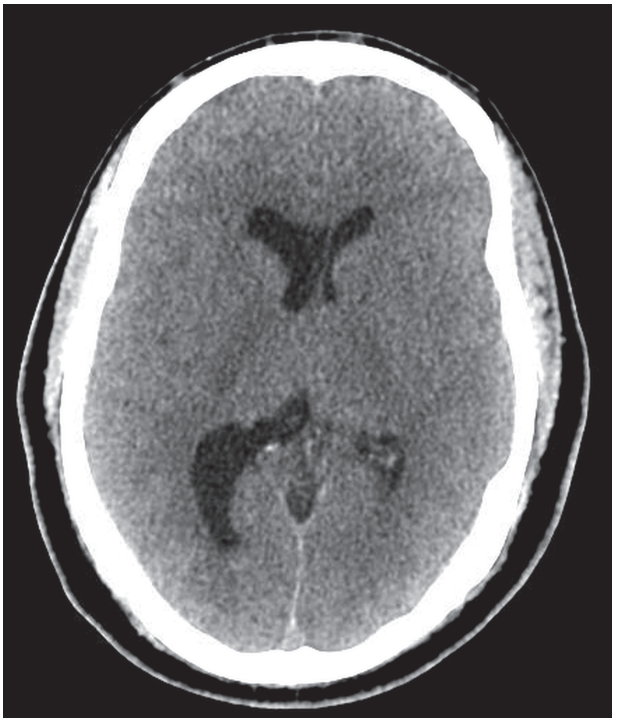

Figure 8: CT head (contrast). Axial Image: there is lateral ventricular dilatation, asymmetric to the right with evidence of debri in the occipital horn of the right lateral ventricle.

(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.

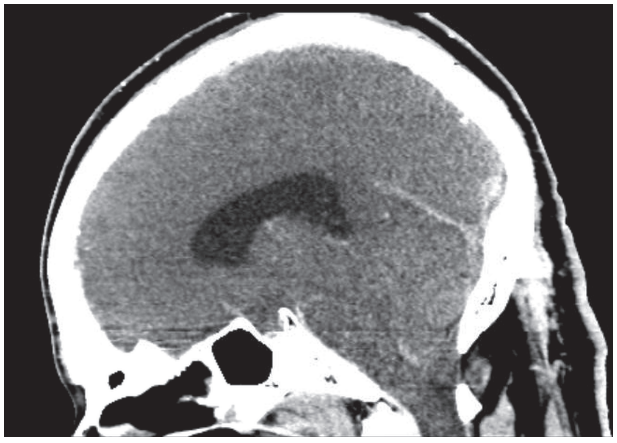

Figure 9: CT Head (Post Contrast). Sagittal image: There is progressive effacement of the suprasellar, pre pontine/ pre medullary cisterns with inferior cerebellar tonsillar descent below foramen magnum.

Lee *et al*. (10) found metastatic infection was significantly associated with infection caused by rmpA positive strains, an APACHE II score of ≥20 and septic shock in 110 cases of hvKP CA-PLA. Mortality was associated with metastatic infection and gas within the abscess, features present in our case, and acute respiratory failure.

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.

FUNDING

No funding provided for this case report.

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.

REFERENCES

1. Rossi B, Gasperini ML, Leflon-Guibout V, Gioanni A, de Lastours V, Rossi G, *et al*. Hypervirulent *Klebsiella pneumoniae* in cryptogenic liver abscesses, Paris, France. *Emerg Infect Dis* 2018;**24**:221–229.
2. Siu LK, Yeh KM, Lin JC, Fung CP, Chang FY. *Klebsiella pneumoniae* liver abscess: a new invasive syndrome. *Lancet Infect Dis* 2012;**12**:881–887.
3. Catalan-Najera JC, Garza-Ramos U, Barrios-Camacho H. Hypervirulence and hypermucoviscosity: two different but complementary *Klebsiella* spp. phenotypes? *Virulence* 2017;**8**:1111–1123.
4. Decré D, Verdet C, Emirian A, Le Gourrierec Petit JC, Offenstadt G *et al*. Emerging severe and fatal infections due to *Klebsiella pneumoniae* in two university hospitals in France. *J Clin Microbiol* 2011;**49**:3012–3014.
5. Zhang Y, Zhao C, Wang Q, Wang X, Chen H, Li H, *et al*. High prevalence of hypervirulent *Klebsiella pneumoniae* infection in China geographic distribution, clinical characteristics, and antimicrobial resistance. *Anitmicrob Agents Chemother* 2016;**160**:6115–6120.
6. Li J, Ren J, Wang W, Wang G, Gu G, Wu X, *et al*. Risk factors and clinical outcomes of hypervirulent *Klebsiella pneumoniae* induced bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2018;**37**:679–689.
7. Su SC, Siu LK, Ma L, Yeh KM, Fung CP, Lin JC, *et al*. Community-acquired liver abscess caused by serotype K1 *Klebsiella pneumoniae* with CTX-M-15-type extended-spectrum beta-lactamase. *Antimicrob Agents Chemother* 2008;**52**:804–805.
8. Rafat C, Messika J, Barnaud G, Dufour N, Dufour F, Billard-Pomarès T, *et al*. Hypervirulent Klebsiella pneumoniae, a 5-year study in a French ICU. *J Med Microbiol* 2018;**67**:1083–1089.
9. Moore R, O'Shea D, Geoghegan T, Mallon PW, Sheehan G, *et al*. Community-acquired *Klebsiella pneumoniae* liver abscess: an emerging infection in Ireland and Europe. *Infection* 2013;**41**:681–686.
10. Lee SS, Chen YS, Tsai HC, Wann SR, Lin HH, Huang CK, *et al*. Predictors of septic metastatic infection and mortality among patients with *Klebsiella pneumoniae* liver abscess. *Clin Infect Dis* 2008;**47**:642–650.