

Bilateral Endogenous Endophthalmitis as an Initial Presentation of *Klebsiella pneumoniae* Bacteremia in Advanced Hepatocellular Carcinoma

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Authors' contributions

This work was carried out in collaboration between both authors. Author RCC wrote the first draft of the manuscript. Authors RCC and TAK managed the literature searches and author TAK revised it critically for important intellectual content. Both authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Aims: To report a case of *Klebsiella pneumoniae* bacteremia presenting as bilateral endogenous endophthalmitis in a patient with advanced hepatocellular carcinoma and liver failure.

Presentation of Case: We describe a 55 year-old man with diabetes, Hepatitis B, metastatic hepatocellular carcinoma with liver failure who presented with sudden, painful, bilateral rapid loss of vision accompanied with hypopyon, intense anterior chamber fibrinous reaction and vitritis. Systematic workup revealed bilateral endogenous *K. pneumoniae* endophthalmitis secondary to hepatobiliary sepsis. Conservative management with systemic piperacillin/tazobactam, intravitreal and topical ceftazidime and vancomycin led to successful sepsis control, however visual outcome was dismal.

Discussion: *Klebsiella* endogenous endophthalmitis has become extremely prevalent in southeast Asia, most commonly occurring as a metastatic complication of pyogenic liver abscess. Early systemic and intravitreal antibiotics remain the cornerstone of its management. Despite adequate treatment, visual prognosis is grave.

Conclusion: This highlights the rapidly destructive nature of this virulent organism. Clinicians must

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be mindful that endophthalmitis can be the initial presenting sign of *Klebsiella* bacteremia and the search for a primary infective source is paramount. Identification of prognostic factors for poor vision following an attack allows early intervention, in hope to improve patient outcomes.

Keywords: *Klebsiella pneumoniae*; bilateral; endogenous endophthalmitis; bacteremia.

1. INTRODUCTION

Endogenous endophthalmitis, also termed metastatic endophthalmitis results from hematogenous spread of pathogens from a remote primary site across the blood ocular barrier to affect the internal structures of the eye. *Klebsiella pneumoniae* is now recognized as the leading cause of endogenous endophthalmitis in Southeast Asia, accounting for up to 60% of cases in this region, especially in the presence of pyogenic liver disease [1-3]. This is in vast contrast to western countries like Europe, United States and Australia where *K. pneumoniae* is the causative organism in only 3-5% of endogenous endophthalmitis cases [4]. This case report highlights the rising prevalence of invasive *Klebsiella* infection in Asia and its known risk factors.

2. PRESENTATION OF CASE

A 55 year-old Malay gentleman, presented to the emergency department of a tertiary hospital in the city he lived in, complaining of bilateral, painful sudden reduced vision and sticky discharge for two days, worse on the left compared to the right eye. There was associated fever and lethargy for a week. He had a background of type 2 diabetes mellitus, Hepatitis B infection, newly diagnosed advanced hepatocellular carcinoma with liver failure (Child-Pugh class B) and lung base metastasis. The past medical history and family history was negative for autoimmune conditions nor thyroid dysfunction. Prior to this episode, he denied similar episodes of painful red eye in the past and there was no history of any eye trauma, contact lens use or eye surgery. Premorbidly, our patient did not have any vision problems and has never undergone treatment for diabetic retinopathy either.

The right vision on presentation was light perception in all quadrants and there was no light perception in the left eye. An initial ophthalmic examination revealed bilaterally injected conjunctivas, with chemosis on the left. Both corneas were edematous and there was no

evidence of infiltrates or gross keratic precipitates. He had severe anterior uveitis bilaterally with dense fibrin and hypopyon. There was no view of iris details nor of the fundus in either eyes due to the cloudy corneas and dense inflammation in the anterior chambers. The intraocular pressures in the right and left eyes were 22 mmHg and 23 mmHg respectively. The lids in both eyes, however, were not swollen and there was no proptosis. An ultrasound scan (B-scan) of both eyes revealed dense vitritis, with no evidence of retinal detachment or traction.

Our patient was treated empirically for sepsis with bilateral endogenous endophthalmitis. He received intravenous piperacillin/tazobactam (Tazosin) 4.5 g tds, alongside intravitreal ceftazidime 2.25 mg/0.1 ml and vancomycin 1 mg/0.1 ml. Intensive hourly topical ceftazidime and vancomycin was also commenced.

Laboratory parameters showed marked neutrophilic leukocytosis (53.6×10^9) and elevated C-reactive protein 21.5 µg/dl. Blood and bilateral vitreous tap cultures yielded *Klebsiella pneumoniae*, sensitive to piperacillin/tazobactam, ceftazidime, cefuroxime and amoxicillin/clavulanate. A computerized tomography (CT) scan of the abdomen showed multiple hypodense necrotic areas and air pockets within the large, multinodular tumour mass occupying the entire left lobe of the liver (Fig. 1).

He showed good response to treatment and was afebrile after 48 hours. Leukocytosis reduced to 21.8×10^9 after five days. Surgical option of bilateral vitrectomy was offered to the patient however was declined due to the high risk from general anaesthesia and the patient's unwillingness to undergo the surgery under local anaesthesia. A total of six doses of intravitreal ceftazidime and vancomycin were given at 72-hour intervals, after which our patient refused any further injections. Topical steroids 4-hourly were also commenced. By two weeks, there was clinical improvement noted as evidenced by gradual resolution of the conjunctival inflammation, hypopyon and fibrin

(Fig. 2a and 2b). Our patient also reported drastic reduction in eye pain. Vision in both eyes, however, remained the same i.e. light perception in the right and no light perception in the left.

Systemic antibiotics were continued for three weeks and subsequently downgraded to oral cefuroxime, as he remained afebrile and blood cultures twice repeated were negative.

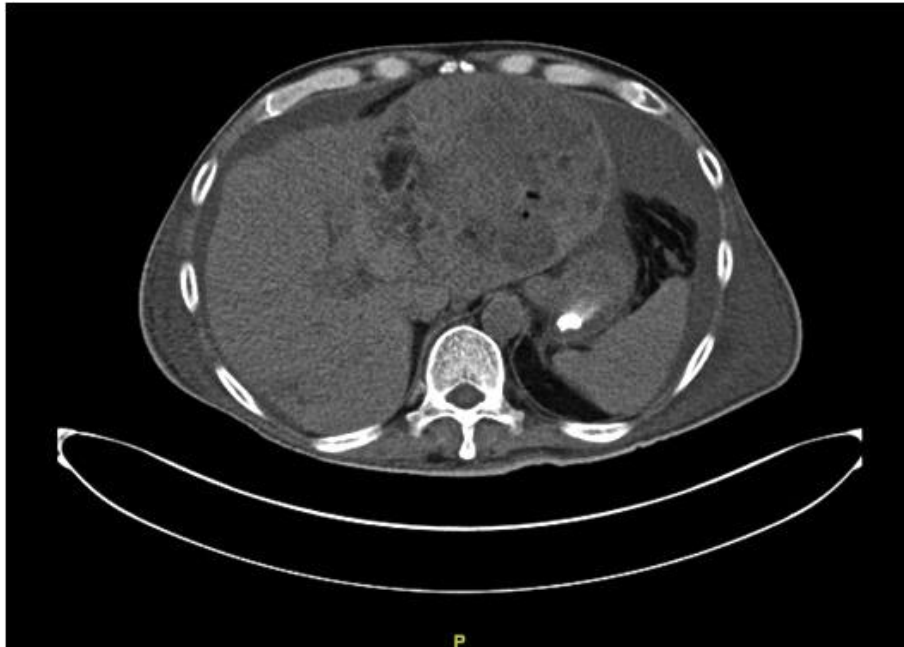


Fig. 1. Large multinodular heterogeneously enhancing mass occupying the entire left lobe of liver with multiple necrotic areas and air pockets within, suggestive of infected tumour

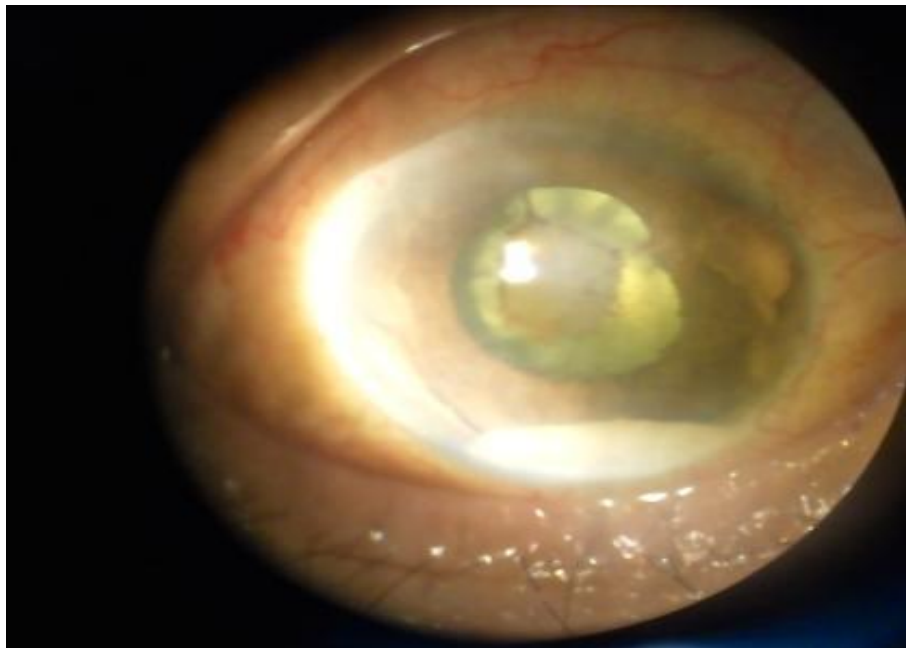


Fig. 2a. Right eye showing contracting pupillary fibrin and hypopyon

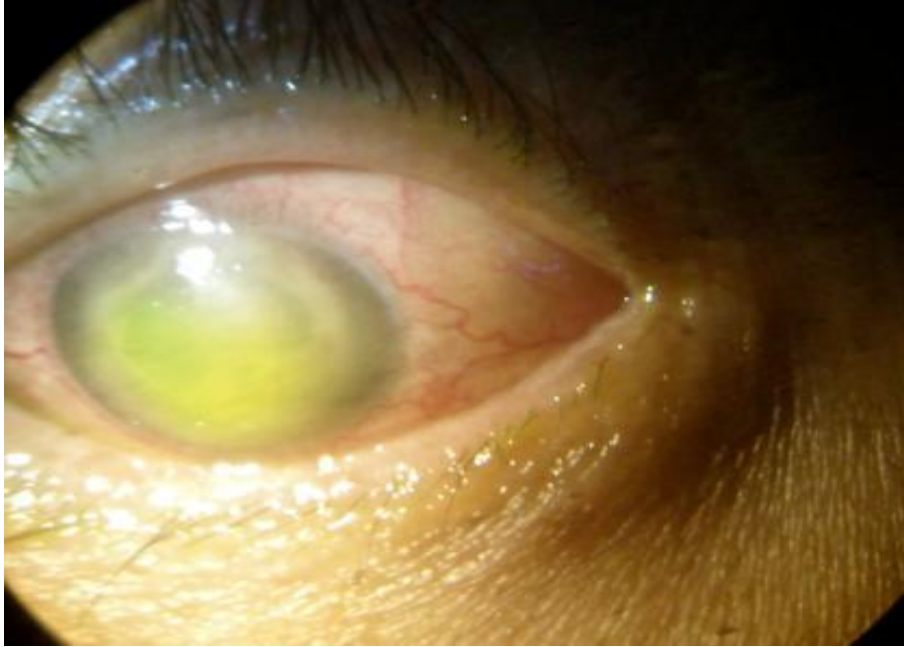


Fig. 2b. Left eye conjunctiva is less injected with resolved chemosis. Anterior chamber fibrinous material reduced, revealing superior pupillary margins. Central large corneal epithelial defect present

Topical antibiotics were also tapered to two hourly since ocular infection appeared to be under control, prior to discharge home for palliative care after one month of hospitalization. Our patient eventually succumbed to liver failure secondary to advanced hepatocellular carcinoma three weeks after discharge. He had no evidence of worsening ocular infection within this period however.

3. DISCUSSION

Klebsiella pneumoniae is the second leading cause of community acquired and nosocomial Gram-negative bacteremia, after *Escherichia coli* [5].

Ko et al. [6] reports significant global differences in clinical patterns of *K. pneumoniae* bloodstream infection. Although pneumonia was found to be the commonest infection site worldwide, there was a distinctive syndrome of liver abscess in conjunction with *Klebsiella* bacteremia almost exclusive to cases in Taiwan. This is resonated by more than 900 case reports of *K. pneumoniae* liver abscesses in Taiwan over the past decade. Specific organism virulence factors such as K1 and K2 capsular serotype, mucoid phenotype and aerobactin production have been implicated

to account for this geographic difference in disease spectrum [4,7,8].

First described in Taiwan during the 1980s, *Klebsiella* invasive syndrome is defined as *K. pneumoniae* liver abscess with extrahepatic complications including endophthalmitis, meningitis and necrotizing fasciitis. Subsequent case reports in other Southeast Asian countries including Singapore, Hong Kong, Korea, Vietnam and China have highlighted the rapid emergence of this invasive entity. Outside Asia, isolated reports on similar presentations have been reported in North and South America [8] Europe [9], Germany [10] and Qatar [11].

Klebsiella endogenous endophthalmitis (EE) is one of the most feared metastatic complication in invasive *Klebsiella* syndrome. In up to 4.9% of cases, ocular symptoms may precede diagnosis of hepatobiliary sepsis [2,12,13], like in our case. The reported risk of developing EE in the presence of *Klebsiella* liver abscess ranges from 3-7.8%. A review by Sheu et al. [14] found 42 individuals (53 eyes) out of 602 patients (6.9%) with pyogenic *Klebsiella* liver disease had developed EE, of which 11 patients (26.1%) experienced bilateral involvement.

Diabetes mellitus has been consistently implicated as a major risk factor for the development of EE in *Klebsiella* bacteremia, especially in cases with poor glycaemic control. This is due to impaired chemotactic and phagocytosis mechanisms by polymorphonuclear leukocytes [14-16]. Sng et al. [2] however had previously reported that diabetes and other comorbid pathologies were not risk factors for endophthalmitis in *K. pneumoniae* bacteraemia.

In a case-control study of 133 patients, definite risk factors for *Klebsiella* EE were hepatic abscess and disseminated intravascular coagulation. Additional risk factors included a lower white cell count at presentation and a longer interval between onset of symptoms and administration of systemic antibiotics [2]. In our patient, significant associations for development of metastatic endophthalmitis are underlying diabetes, hepatobiliary sepsis and delayed presentation of 2 days between onset of ocular symptoms and administration of intravenous antibiotics.

The management of *Klebsiella* EE is challenging for a variety of reasons. Currently, there are no guidelines available, specifically on the role of vitrectomy. In contrast to post-operative endophthalmitis, prompt administration of intravenous antibiotics is key to address the primary source of infection, which in Southeast Asia is of hepatobiliary origin in up to 77.5% of cases [1,3,13,14,17].

The choice of antimicrobial should be guided according to in-vitro sensitivity results and clinical response. Successfully treated cases in the literature employed first to third generation cephalosporins, aminoglycosides and anti-pseudomonal penicillins [8]. Antibiotics need to be continued for at least 2-3 weeks until systemic infection has been eradicated for certain. In conjunction to this, intravitreal antibiotics such as amikacin 400 µg/0.1 ml, gentamicin 0.05 mg/0.1 ml, ceftazidime 2.25 mg/0.1 ml and vancomycin 1 mg/0.1 ml have been used [14,15].

Pars plana vitrectomy in endogenous *Klebsiella* endophthalmitis can reduce the bacterial load and inflammatory mediators within the vitreous cavity, as well as enhance ocular penetration of antibiotics [4,14]. In some cases series, early vitrectomy was shown to save eyes from enucleation or evisceration [14,18]. However, due to poor systemic conditions these patients present with, combined with high risk for general

anesthesia, early vitrectomy is not always feasible [1,17]. The shift towards 23-gauge and 25-gauge transconjunctival sutureless vitrectomy offers increased patient comfort, shorter operation duration and performance under local anaesthesia. Hence, small gauge vitrectomy may be a solution for ill and high-risk patients who are not fit for general anaesthesia and long operations [17]. Perhaps early posterior vitrectomy under local anaesthesia could have improved visual outcome in our patient. To date, most studies have concluded no significant difference in visual outcome between conservative management and vitrectomy [13-15].

Over the years, despite improved recognition and aggressive treatment of endogenous *Klebsiella* endophthalmitis, the final visual outcome remains grim. In a case series of 71 eyes, 41 patients (57.6%) had a final vision of no light perception [13]. Experimental animal models have demonstrated rapid and irreversible destruction of retinal photoreceptors occurred as early as 48 hours of infection, due to the extremely virulent nature of *K. pneumoniae* [14]. Ang et al. [13] revealed the prognostic factors for poor visual outcomes to be presence of hypopyon, unilateral involvement, short time interval from onset of sepsis to ocular symptoms (4 days or less) and panophthalmitis. Identification of these poor prognostic factors allows clinicians to intervene early, in hope to improve outcomes in such patients.

4. CONCLUSION

In summary, this case highlights the well-known risk factors for *K. pneumoniae* bacteremia including diabetes, liver failure and malignancy. Ophthalmologists faced with endophthalmitis in a patient of Asian decent with the mentioned risk factors must actively search for a primary infective focus, most commonly *Klebsiella* hepatobiliary sepsis, as ocular disturbances may be the first presenting sign. Although drainage of pyogenic liver abscesses is advocated to control *Klebsiella* bacteremia, not all patients will be suitable candidates. This is particularly so in our case of advanced hepatocellular carcinoma with superimposed necrotic areas within the tumour. Despite this, our patient recovered from sepsis with intensive and prolonged systemic antibiotics. With conservative management of the bilateral endophthalmitis, he did not require evisceration or enucleation either. However, final visual outcome was poor, further emphasizing the

grave prognosis of this increasingly prevalent entity. Further research on the exact virulence factors in *K. pneumoniae* strains in Southeast Asia is crucial and vaccination in high-risk groups could potentially be achieved in the near future.

CONSENT

All authors declare that written informed consent was obtained from the patient and his wife for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Wong JS, Chan TK, Lee HM, Chee SP. Endogenous bacterial endophthalmitis-An east asian experience and a reappraisal of a severe ocular affliction. *Ophthalmology*. 2000;107(8):1483-1491.
2. Sng CCA, Jap A, Chan YH, Chee SP. Risk factors for endogenous *Klebsiella* endophthalmitis in patients With *Klebsiella* Bacteremia: A Case-control Study. *Br J Ophthalmol*. 2008;92:673-677. DOI: 10.1136/bjo.2007.132522.
3. Chen YJ, Kuo HK, Wu PC, Kuo ML, Tsai HH, Liu CC, et al. A 10-Year Comparison of Endogenous Endophthalmitis Outcomes: An East Asian Experience with *Klebsiella pneumoniae* Infection. *Retina*. 2004;24(3):383-390.
4. Sridhar J, Flynn HW, Kuriyan AE, Dubovy S, Miller D. Endophthalmitis caused by *Klebsiella* species. *Retina*. 2014; 34(9):1875-1881.
5. Meatherall BL, Gregson D, Ross T, Pitout J, Laupland K. Incidence, risk factors and outcomes of *Klebsiella pneumoniae* bacteremia. *The American Journal of Medicine*. 2009;122:866-873. DOI: 10.1016/j.amjmed.2009.03.034.
6. Ko WC, Paterson DL, Sagnimeni AJ, Hansen DS, Gottberg AV, Mohapatra S, et al. Community-acquired *Klebsiella pneumoniae* bacteremia: Global differences in clinical patterns. *Emerging Infectious Disease*. 2002;8(2):160-166.
7. Yu VL, Hansen DS, Ko WC, Sagnimeni A, Klugman FP, Gottberg AV, et al. Virulence characteristics of *Klebsiella* and clinical manifestations of *K. pneumoniae* bloodstream infections. *Emerging Infectious Diseases*. 2007;13(7):986-993.
8. 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.
9. Sobirk SK, Struve C, Jacobsson SG. Primary *Klebsiella pneumoniae* liver abscess with metastatic spread to lung and eye, a North-European case report of an emerging syndrome. *Open Microbiol J*. 2010;4:5-7.
10. Bilal S, Volz MS, Fiedler T, Podschun R, Schneider T. *Klebsiella pneumoniae*-induced liver abscesses, Germany. *Emerg Infect Dis*. 2014;20(11):1939-1940. DOI: 10.3201/eid2011.140149.
11. Al Ani AARM, Elzouki AN, Rahil A, Al-Ani F. Endogenous endophthalmitis and liver abscess syndrome secondary to *Klebsiella pneumoniae*: Report of Three Cases from Qatar. *Asian Pacific Journal of Tropical Biomedicine*. 2015;5:930-935.
12. Iglesias APB, Cabeza MIP, Pardo MJR, Castano M. Endogenous endophthalmitis as a first clinical manifestation of *Klebsiella* sepsis. The Importance of an Early Diagnosis. *Arch Soc Esp Oftalmol*. 2011;86(12):412-414.
13. Ang M, Jap A, Chee SP. Prognostic factors and outcomes in endogenous *Klebsiella pneumoniae* endophthalmitis. *Am J Ophthalmol*. 2011;151:338-344.
14. Sheu SJ, Kung YH, Wu TT, Chang FP, Horng YH. Risk factors for endogenous endophthalmitis secondary to *Klebsiella pneumoniae* liver abscess-20 year experience in Southern Taiwan. *Retina*. 2011;31(10):2026-2031.
15. Chen KJ, Hwang YS, Chen YP, Lai CC, Chen TL, Wang NK. Endogenous *Klebsiella* endophthalmitis associated with *Klebsiella pneumoniae* pneumonia. *Ocular Immunology and Inflammation*. 2009; 17:153-159. DOI: 10.1080/09273940902752250.
16. Lin YT, Wang FD, Wu PF, Fung CP. *Klebsiella pneumoniae* liver abscess in

- diabetic patients: Association of glycaemic control with the clinical characteristics. BMC Infectious Diseases. 2013;13:56. DOI: 10.1186/1471-2334-13-56.
17. Lee SH, Um TW, Joe SG, Hwang JU, Kim JG, Yoon YH, et al. Changes in the clinical features and prognostic factors of endogenous endophthalmitis-fifteen years of clinical experience in Korea. Retina. 2012;32:977-984.
18. Yoon YH, Lee SU, Sohn JH, Lee SE. Result of early vitrectomy for endogenous *Klebsiella pneumoniae* endophthalmitis. Retina. 2003;23:366-370.

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