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Case Study **Bilateral Endogenous Endophthalmitis As An Initial Presentation of *Klebsiella Pneumoniae* Bacteremia in Advanced Hepatocellular Carcinoma**

ABSTRACT

Keywords: KlebsiellaPneumoniae, bilateral, endogenous endophthalmitis, bacteremia

Aims: To report a case of *KlebsiellaPneumoniae* 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, 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 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.

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. *Klebsiellapneumoniae* 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. [1,2,3] 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.

PRESENTATION OF CASE

A 55 year-old Malay man presented to the emergency department complaining of bilateral sudden reduced vision and sticky discharge for 2 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.

Presenting vision was light perception on the right, and no light perception on the left. An initial ophthalmic examination revealed bilaterally injected conjunctivas, with chemosis on the left. His corneas were hazy. There was severe anterior uveitis, dense fibrinous material in the anterior chambers and hypopyon, much more marked in the left eye. Intraocular pressures in the right and left eyes were 22mmHg and 23 mmHg respectively. No fundus view was available. B-scan ultrasound of both eyes revealed dense vitritis. The lids were not swollen and there was no proptosis.

Our patient was treated empirically for sepsis with bilateral endogenous endophthalmitis. He received intravenous Piperacillin/Tazobactam (Tazosin) 4.5g tds, alongside intravitrealCeftazidime 2.25mg/0.1ml and Vancomycin 1mg/0.1ml. Intensive hourly topical Ceftazidime and Vancomycin was also commenced.

Laboratory parameters showed marked neutrophilic leukocytosis (53.6×10^9) and elevated C-reactive protein 21.5µg/dl. Blood and bilateral vitreous tap cultures yielded *KlebsiellaPneumoniae*, sensitive to Piperacillin/Tazobactam, Ceftazidime, Cefuroxime and Amoxycillin/Clauvulanate. A computerized tomography (CT) scan of the abdomen showed multiple hypodense necrotic areas and air pockets within the large, multinodulartumour mass occupying the entire left lobe of the liver. (Fig. 1)

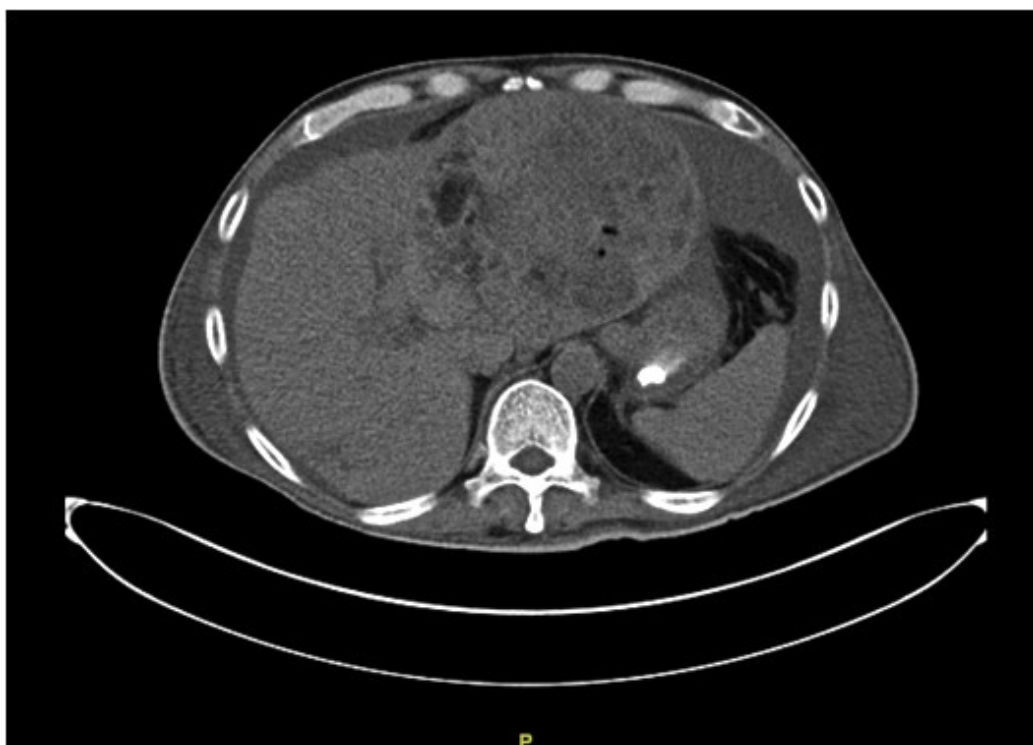


Fig. 1

He showed good response to treatment and was afebrile after 48 hours, and leukocytosis reduced to 21.8×10^9 after 5 days. Bilateral vitrectomy was not performed due to significant mortality risk from general anaesthesia, and refusal from his family members. A total of 6 doses of intravitreal Ceftazidime and Vancomycin was given at 72-hour intervals, after which our patient refused further injections. Despite conservative management, there was evident improvement in the eye signs. At 2 weeks, the conjunctiva became less injected, while the hypopyon and fibrin showed gradual reduction. (Fig. 2a and 2b) Vision remained the same bilaterally.

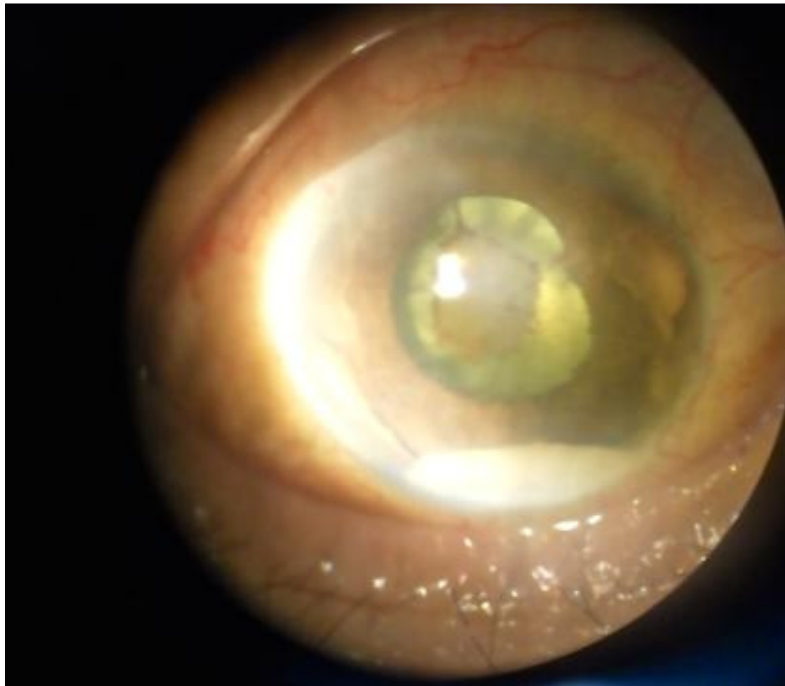


Fig. 2a

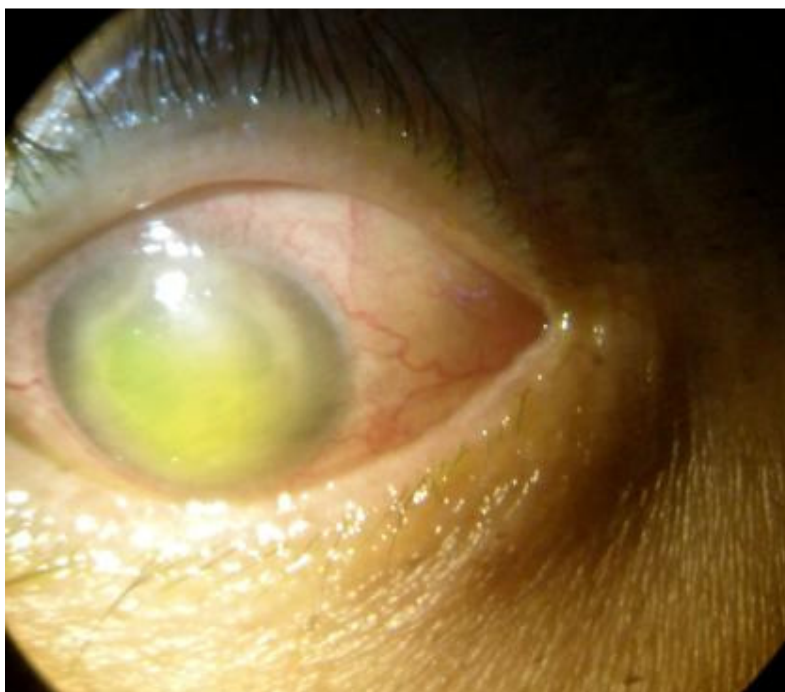


Fig. 2b

Systemic antibiotics were continued for 3 weeks and subsequently downgraded to oral Cefuroxime. Topical antibiotics were also tapered to 2 hourly prior to discharge home for palliative care after 1 month of hospitalization.

DISCUSSION

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

Ko et.al. 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.^[6] 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. 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.^[14]

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.^[14,15,16] Sng et.al. however had previously reported that diabetes and other comorbid pathologies were not risk factors for endophthalmitis in *K.pneumoniae* bacteraemia.^[2]

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/0.1ml, Gentamicin 0.05 mg/0.1ml, ceftazidime 2.25 mg/0.1ml and vancomycin 1mg/0.1ml have been used.^{[Error! Bookmark not defined.,^{14]}}

Pars planavitrectomy 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] In addition, most studies have concluded no significant difference in visual outcome between conservative management and vitrectomy.^[13] **Error! Bookmark not defined.**^[14]

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. 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.^[13]

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. A copy of written consent is available for review by the Editorial office/ Chief Editor/ Editorial Board members of this journal.

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FIGURE LEGENDS

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.

