Metastatic Klebsiella Infection: A Case Report

Jacklyn So-Cabahug, M.D.*; and Jennifer Justice Manzano, M.D.*

Abstract

Introduction: A new hypervirulent (hypermucoviscous) variant of *Klebsiella pneumoniae* (*K. pnuemoniae*) had emerged. It has shown ability to cause serious infection in healthy ambulatory hosts as well as infect unusual sites. Though there have been numerous studies on severe infection by *K. pneumoniae,* little data has been documented on such infections involving *Klebsiella oxytoca*. (*K. oxytoca*). It is capable of causing metastatic spread of the infection even in healthy young individuals. This report was written to describe the clinical spectrum of a case of metastatic *Klebsiella* infection.

Case presentation: We illustrate a case of a 73-year-old diabetic and hypertensive female presenting with headache and eye discharge. She was initially managed as the case of conjunctivitis as out-patient. After three weeks of topical ophthalmic antibiotics, she developed decrease in sensorium leading to her eventual admission. Workup pointed towards a disseminated infection to the eye, brain, and urinary tract. The patient was placed on broad-spectrum antibiotics and a vitreous tap was done. However, the patient's sensorium decreased further, and was eventually intubated and started on inotropes. The indolent course of the disease, which unfortunately led to the demise of the patient, directed the attending physicians to suspect a more virulent infection.

Discussion: Infection by hypervirulent variant of *Klebsiella* has been classically known to be nosocomial and opportunistic in nature. But cases have also been reported from the community setting. A common denominator in this population is that they are usually immunocompromised as in the case of our patient being elderly and diabetic. Unfortunately, there are no molecular or biochemical markers being used in the clinical setting to identify this strain. Hence, the attending physicians had to rely on the presentation of metastatic disease to diagnose our patient.

Conclusion: Early diagnosis, appropriate antibiotic treatment and drainage are keys in the management of these cases.

Keywords: metastatic klebsiella, hypermucoviscous, infection, klebsiella spp

Introduction

Klebsiella spp. has been known to be a notorious cause of opportunistic infections in hospitalized patients, but anecdotal data have also noted its presence and capability to be transmitted to a community-based population.[1,2] Currently, a comprehensive understanding of the prevalence of the hypervirulent *Klebsiella* remains wanting.[3] This stems from the lack of an unequivocal genotypic/phenotypic marker(s) to identify the strain. Hence, the identification or the labeling of the infection as that of the hypervirulent strain is based on its clinical features such as the metastatic spread of the infection. This paper reports one such case, in the attempt that the illustration of its identification and management will increase the awareness and index of suspicion of our fellow health care providers of the presentation of the disease. Likewise, it will be a step closer to understanding its epidemiology.

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Case Presentation

A 73-year-old diabetic and hypertensive female was admitted for decrease in sensorium. She claimed to be compliant to maintenance medications, but with a capillary blood glucose (CBG) monitoring range of 180-216 mg/dL.

One month prior to admission (PTA), the patient complained of tolerable left-sided headache, she did not seek consult nor took any medications. Three weeks PTA, she was noted to have matting of eyelashes, with yellowish discharge and itchiness of the left eye. The relative of the patient consulted with an ophthalmologist with a picture of the patient and she was given a combination of tobramycin and dexamethasone ophthalmic drops. One week after

application of the medication, there was a decrease in the yellowish discharge but the patient developed difficulty in opening her eyelids. She consulted with an ophthalmologist who did a culture of the eye discharge which was revealed to be negative for growth. Two days PTA, another culture specimen of the ocular discharge was done which revealed no growth. One day PTA, the patient had an increase in sleeping time. On the day of admission, the patient had loss of appetite, chills, followed simple commands but had no verbal output, prompting the relatives to bring the patient to the emergency room (ER) (Figure 1).

At the ER, the patient's vital signs included blood pressure 110/70 mmHg, body temperature 36.4°, pulse 116 beats/min, breathing 18 cycles/min. She was awake, followed commands, with a glasgow coma scale (GCS) of 12 E4V2M6. Her palpebral conjunctivae were slightly pale, there was matting of the eyelashes, yellowish discharge, with membranous formation of the cornea and swelling of the eyelid on the left eye (Figure 2). The external ear canal was not hyperemic and there was no aural or nasal discharge. Her lips were dry and there were dental caries (Figure 3). Chest examination revealed no adventitious breath sounds, tachycardia, but no audible murmurs. There was onychomycosis on the right thumb (Figure 4). The neurologic examination are as follows: extraocular muscles (EOMs) were full and equal, (+) shallow left nasolabial fold, intact gag, tongue midline, manual muscle test (MMT) was 2/5 on the left extremities and 4/5 on the right extremities, normal bulk and tone of muscles, deep tendon reflex (DTR) +2 on all extremities, no nystagmus, neck was supple, there was no papilledema. The initial impression was diabetic emergency vs. cerebrovascular accident, endophthalmitis left, complicated urinary tract infection (UTI), anemia, hypertensive cardiovascular disease, and type 2 diabetes mellitus (DM), and onychomycosis.

The ER laboratory workup including a complete blood count (CBC) revealing leukocytosis of 14.1 with neutrophilic predominance (85%) and anemia with a hemoglobin (Hgb) of 7.1 mg/dL with and MCV 83.1 fl and MCH 28.6 pg. The

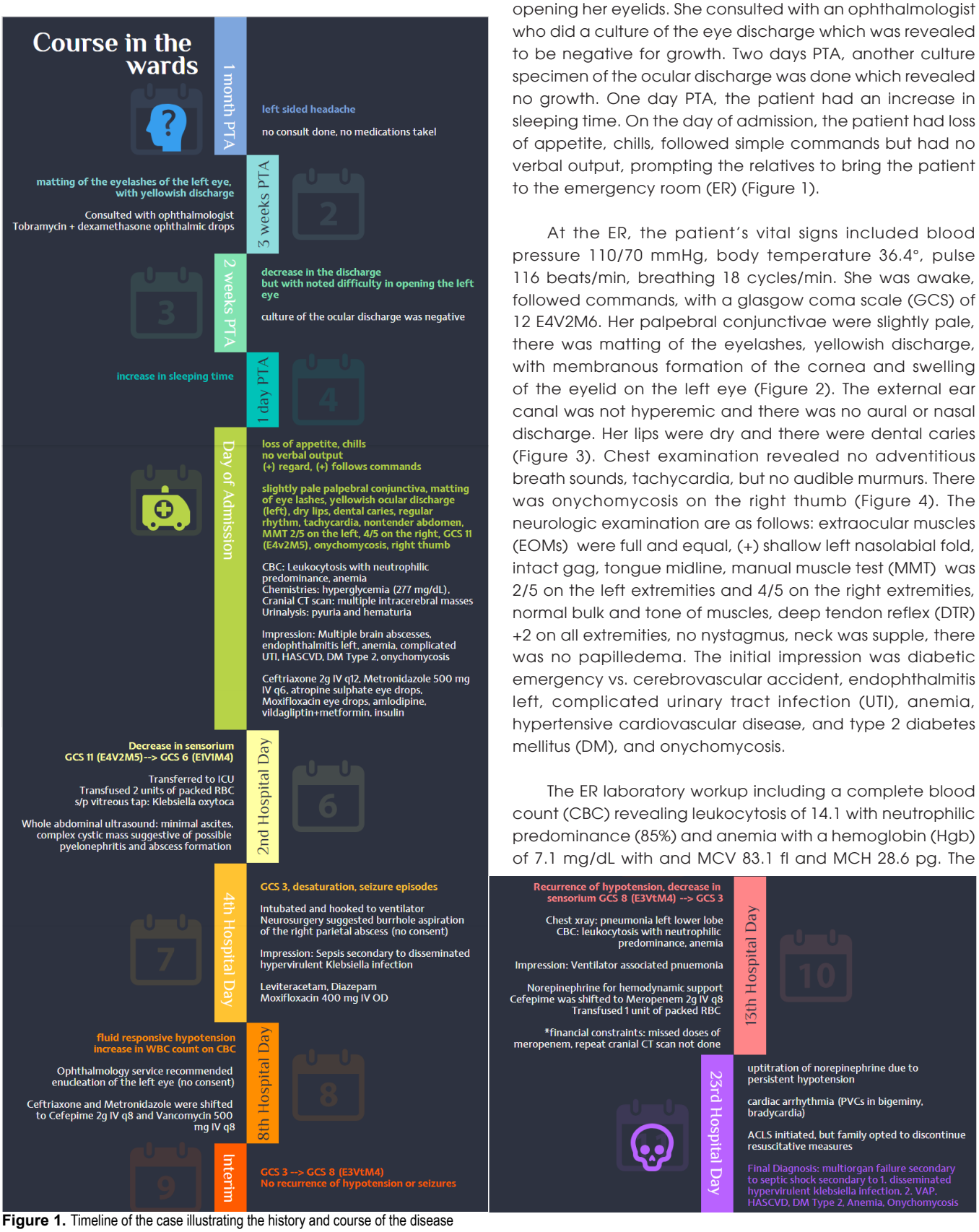

Figure 1. Timeline of the case illustrating the history and course of the disease

transfusion of two units of packed RBC raised the Hgb to 10.6. The chest x-ray revealed pulmonary tuberculosis (PTB) with cicatricial changes of the left upper lung, and atherosclerotic aorta. PTB was ruled out with a negative sputum AFB smear. There was hyponatremia with a sodium (Na) of 127, corrected Na of 131 and serum osmolality of 286; creatinine was elevated at 1.14 which was attributed to dehydration and infection, though the BC ratio (17) was normal. The patient was hydrated with normal saline resulting in the normalization of the creatinine. She was also given regular insulin and vildagliptin 50 mg + metformin 500 mg OD to control hyperglycemia (277 mg/dl). The non-enhanced brain CT (Figure 5 and 6) showed multiple intercerebral masses at the bilateral parietal and right temporal lobe, chronic lacunar infarct on the right thalamus and left lentiform nucleus (considering abscesses vs. metastasis), chronic periventricular white matter microvascular ischemic changes, cerebrocerebellar atrophy, arteriosclerosis, hypoplastic frontal sinuses, consider scleritis and conjunctivitis left.

Other workup revealed: complicated UTI (urinalysis: WBC 9092.82/hpf, bacteria of 802.94/hpf, and whole abdominal ultrasound (Figure 7): minimal ascites, prominent left kidney with perinephric fluid and a complex cystic mass suggestive of possible pyelonephritis with possible abscess formation. A neoplasm cannot be ruled out), blood and urine culture were negative for growth, while the electroencephalogram (EEG) revealed severe diffuse slowing of the background activity indicative of severe diffuse cerebral dysfunction. There was also noted hypomagnesemia which was corrected, while amlodipine 10 mg OD was given for elevated blood pressure.

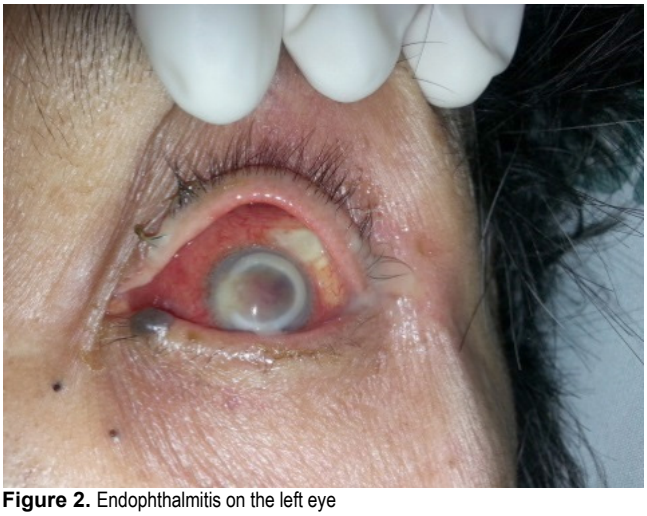

Figure 2. Endophthalmitis on the left eye

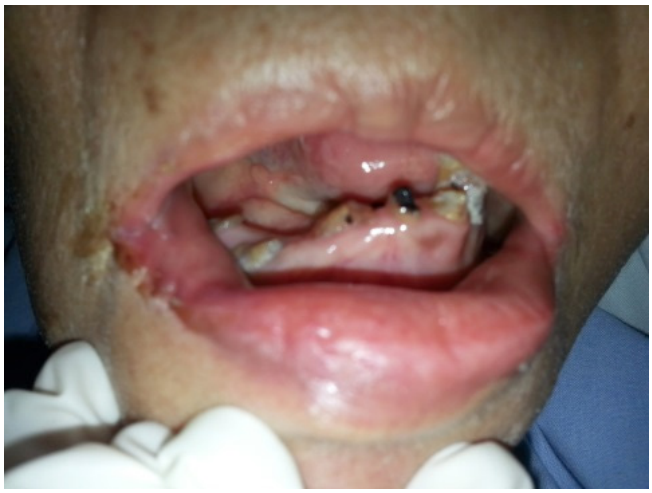

Figure 3. Dental caries

Urgent consultation was sought from the neurology and ophthalmology services. The neurologist started ceftriaxone

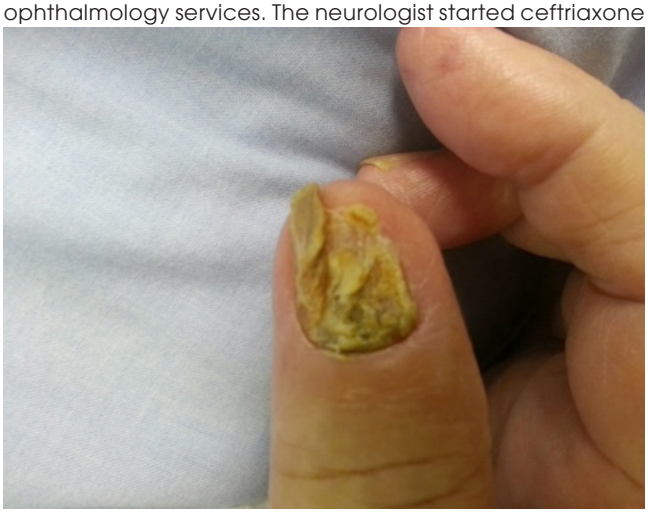

Figure 4. Onycomycosis

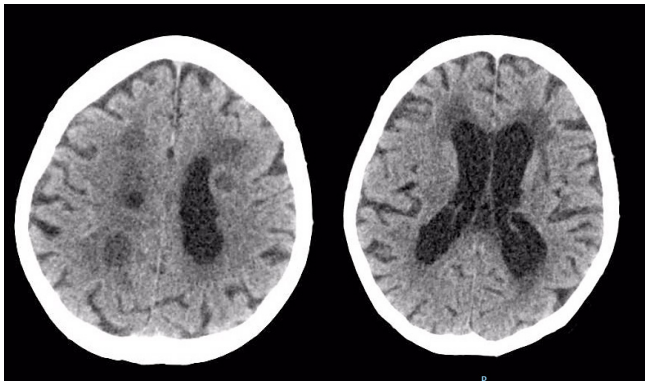

Figure 5 and 6. Non enhanced CT scan revealing multiple intercerebral masses

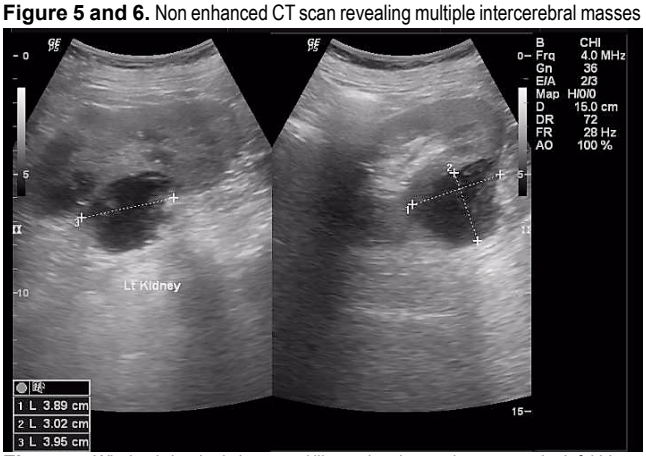

Figure 7. Whole abdominal ultrasound illustrating the cystic mass on the left kidney

2g IV every 12 hours and metronidazole 500 mg IV every six hours as empiric treatment for community acquired brain abscess which can also cover for the complicated UTI. Ophthalmology service started atropine sulphate eye drops (one to two drops on the affected eye every eight hours) and moxifloxacin 0.5% eye drops (one drop on the affected eye every three hours) for the endophthalmitis. The attending physician was managing the patient based on the impression of sepsis secondary to multiple intercerebral abscesses, (community acquired) complicated UTI, endophthalmitis left eye, anemia (normocytic, normochromic), hypertensive atherosclerotic cardiovascular disease (HASCVD), and type 2 DM.

On the second hospital day, the patient's sensorium decreased from GCS 12 (E4V2M6) to 6 (E1V1M4) hence the patient was transferred to the ICU. She underwent the vitreous tap of the left eye, wherein mucopurulent brown grey fluid was aspirated. Though the vitreous tap was AFB negative, and the Gram stain was also negative for polymorphonuclear cells and microorganisms; the culture revealed *Klebsiella oxytoca* (*K. oxytoca*) sensitive to ceftriaxone, but resistant to ampicillin and ticarcillin.

On the forth hospital day, patient was noted to be GCS 3 with 88% O_2 saturation, hence was intubated and hooked to a mechanical ventilator. There were also noted seizures lasting four seconds presenting as lip smacking with twitching of the left arm. She was given leviteracetam 1 g tab q12 and diazepam for frank seizures. To rule out the possibility of intraventricular rupture as the cause of the deterioration of the mental status of the patient as well as the seizures, a stat repeat cranial CT scan was done, which revealed no change in the intracranial structure. Consultation from the service of neurosurgery provided a recommendation for burrhole aspiration of the right parietal abscess for diagnostic purposes. There was no consent from the family due to the risks of the procedure. Referral to infectious disease was also sought wherein the antibiotics was continued and moxifloxacin 400 mg IV every 24 hours was added. The impression at this point was disseminated hypervirulent *Klebsiella* infection (eye, brain, and kidney).

On the eighth hospital day, patient was noted to have episodes of hypotension (80/40 mmHg) which was responsive to fluid challenge. The WBC count at this point was noted to be increasing in trend (20.6) with neutrophilic predominance (83%). This was interpreted as progression of sepsis hence ceftriaxone and metronidazole were shifted to cefepime 2g IV every eight hours and vancomycin 500 mg IV every eight hours. The service of ophthalmology recommended enucleation of the infected eye once the patient was more stable. Subsequently, there was recurrence of the seizure episodes hence the initiation of oxycarbamazepine 300 mg BID and valproic acid with a loading dose of one gram then maintained at 750 mg q12.

Subsequent hospital days revealed improvement of the sensorium of the patient with a GCS 8 (E3VtM4) and no recurrence of the seizures or hypotensive episodes.

On the 13th hospital day, the patient's condition further deteriorated into septic shock presenting with hypotension that was not responsive to fluid resuscitation. Repeat chest x-ray revealed interval development of pneumonia on the left lower lobe indicative of ventilator associated pneumonia hence cefepime was shifted to meropenem 2g IV every eight hours, while norepinephrine drip was started to maintain the blood pressure and vancomycin was discontinued after seven days. Patient was ideally for repeat cranial CT scan to assess for any changes in the size of the lesions as well as progression of perilesional edema, but the relatives opted to defer due to financial constraints.

The repeat CBC revealed anemia with a Hgb of 8.6, WBC count of 19.7 and neutrophils of 88%. One unit of PRBC was thereby transfused. The episodes of hypoglycemia prompted the adjustment of insulin. Unfortunately, antibiotic therapy was not maximized due to the issue of finances; resulting in missed doses of meropenem. There was also noted episodes of desaturation or increase in oxygen requirement, requiring increase in the FiO_2 support to 100% but eventually decreased to 40% in the subsequent days.

On the 23rd hospital day, the patient remained unarousable, had recurrence of hypotension and norepinephrine drip was adjusted accordingly. With the cessation of the seizures, leviteracetam was decreased to 500 mg BID. On cardiac monitoring there was noted dysrhythmia (premature ventricular contractions in bigeminy with non-sustained ventricular tachycardia), within minutes, patient became bradycardic at 40-50 beats per minute and was gasping, this was immediately followed by cardiopulmonary arrest. ACLS was started, atropine (total of 1 mg) IV was given along with IV doses of epinephrine. This was followed by pulseless ventricular tachycardia (defibrillation with biphasic 100 joules was done) and ventricular fibrillation (defibrillation with biphasic 200 joules four times was done) and finally, asystole. The family of the patient opted to discontinue further resuscitative measures.

Patient expired with a diagnosis of multiorgan failure secondary to septic shock secondary to disseminated hypervirulent *Klebsiella* infection and ventilator associated pneumonia; seizure disorder secondary to intercerebral abscesses; anemia, acute kidney injury secondary to infection; HASCVD, type 2 DM, and onychomycosis on the 24th hospital day, the assessment and management of which was summarized in Table I.

Table I. Assessment and Management

Subjective complaints	Objective findings	Assessment	Management
Elderly female diabetic and hypertensive 4 week history of left sided headache 3 weeks prior noted matting of eyelashes and yellowish discharge of left eye Treated as bacterial conjunctivitis 1 day prior decrease in sensorium On day of consult noted with loss of appetite, no verbal output	BP 110/70, HR 116, RR 18, Temp 36.4°, E4V2M6 Slightly pale palpebral conjunctiva Matting of eyelashes with yellowish discharge OS Dry lips, dental caries Clear breath sounds Regular rhythm No murmur Onychomycosis right thumb MMT 2/5 left, 4/5 right Supple neck, no papilledema Deterioration of sensorium Development of lip smacking and focal seizure left upper extremity as well as hypotension Laboratories CBC: ↑WBC, ↑PMN, ↓Hgb, ↓Hct Na 127, normoosmolar Crea 1.14, BUN 20, CBG 277 CXR: PTB left upper lung, atherosclerotic aorta AFB: negative Urinalysis: ↑WBC, ↑bacteria CT scan: multiple intercerebral masses EEG: diffused slowing of background activity WABUTZ: complex cystic mass, left kidney, consider pyelonephritis Vitreous tap: *Klebsiella oxytoca* sensitive to Ceftriaxone Repeat CXR: interval left lower lobe infiltrates	1. Septic shock secondary to disseminated *Klebsiella* infection, and ventilator associated pneumonia 2. Seizure disorder secondary to intercerebral abscesses 3. Anemia, normocytic, normochromic 4. AKI prob secondary to infection vs dehydration Hyponatremia, isotonic 5. HASCVD 6. DM Type 2 7. Onychomycosis	1. Ceftriaxone 2g IV q12, Metronidazole 500 mg IV q6, later shifted to Cefepime 2g IV q8 and Vancomycin 500 mg IV q8, upon the development of septic shock, cefepime was shifted to Meropenem 2g IV q8, Moxifloxacin 400mg IV OD Norepinephrine drip Moxifloxacin and atropine ophthalmic drops s/p vitreous tap for enucleation OS for burrhole aspiration of the abscess 2. Leviteracetam, diazepam valproic acid and oxycarbamazepine 3. Transfusion 2 units of packed RBC 4. Hydration 5. Amlodipine 6. Vilagliptin+ metformin, insulin

Abbreviations: AAFB – acid fast bacilli, AKI – acute kidney injury, BUN – blood urea nitrogen, CBC – complete blood count, CBG – capillary blood glucose, Crea – serum creatinine, CT – computer tomography, CXR – chest xray, DM – diabetes mellitus, EEG – electroencephalogram, HASCVD – hypertensive atherosclerotic cardiovascular disease, Hct – hematocrit, Hgb – hemoglobin, MMT – manual muscle test, Na – serum sodium, OS – ocular sinister (left eye), PMN – polymorphonuclear cells, PTB – pulmonary tuberculosis, RBC – red blood cells, WABUTZ – whole abdominal ultrasounds, WBC – white blood cells

Discussion

Klebsiella is a member of the Enterobacteriaceae family that was named in honor of the German microbiologist Edwin Klebs.[4] The first specie - *Klebsiella pneumoniae (K. pneumoniae*) described was in 1882 by Friedlander, as an encapsulated bacillus isolated in a patient who died of pneumonia. This organism was implicated as a cause of pneumonia, especially in diabetic patients. It has also been described to cause infection of the urinary tract, biliary tract, osteomyelitis and bacteremia.[3] Another *Klebsiella* specie which has been known to cause nosocomial as well as community acquired infection is the *K. oxytoca* which in the 1950's was thought to be a biogroup of *K. pneumoniae* until DNA relatedness studies distinguished it from *K. pneumoniae*.[4] Members of this genus have capsules composed of complex acidic polysaccharides, essential to its virulence. Of particular virulence are those strains that express capsular type K1 or K2.[5]

The *Klebsiella spp.* are ubiquitous in nature and have two habitats: one being the environment and the other being the mucosal surfaces of mammals such as humans, which they colonize. In humans, *K. pneumoniae* is present as a saphrophyte in the nasopharynx and in the intestinal tract. Because gram negative bacteria don't find good growth conditions on the human skin, *Klebsiella spp* are rarely found there and are at most transient members of the flora.[1] A survey in the 1970's on *Klebsiella* carriage was done involving urban residents, hospital personnel and newly admitted patients showed 30-37% of individuals carried *Klebsiella*. In general, patient colonization by *Klebsiella* increases with length of stay and antibiotic use.[3] There were two species of *Klebsiella* that has been known to cause majority of the infection namely, *K. pneumoniae* and *K. oxytoca*, in a 2-4:1 proportion. Features predisposing to *Klebsiella* infection include extremes of age, chronic alcoholism, diabetes mellitus, chronic renal, cardiac, pulmonary, and neoplastic diseases.[1]

Klebsiella are widely recognized as important opportunistic pathogens in hospital patients, representing three to eight percent of all nosocomial bacterial infections. However, in addition to this data, community acquired *K.*

pneumoniae infections can present with severe clinical manifestations, hence pose as an important public health problem particularly, but not limited to the Asia Pacific Region.[1,2] First, primary bacteremic liver abscess has been described since 1989 in Asia, especially in Taiwan, and in the British Isles.[1,5-8] Second, endophthalmitis, almost exclusively reported from Asia, has now been reported in the United States. The infection has been postulated to be a complication of liver abscess.[1,9] Third, *K. pneumoniae* as the cause of community-acquired bacterial meningitis in adults in Asia, in the absence of association with liver abscess or infections of other body sites.[1] Recently, a new syndrome has been described in the form of a renal abscess syndrome causing metastatic lesions to the brain, eyes and lungs. The patient was Hispanic, diabetic, and made complete recovery with IV antibiotics.[10]

Given this numerous data on *K. pneumoniae*, sparse literature has been made for infections on *K. oxytoca*. This specie can also cause community acquired infections but not as common as *K. pneumoniae*. Notable few include *Klebsiella* bacteremia in patients after undergoing hematopoietic stem cell transplant who were immunocompromised due to their underlying blood disorder. These patients were treated with IV carbapenems and aminoglycosides.[11] Another report revealed bacteremia associated with patients with chronic pancreatitis and history of gastric cancer. These patients were treated with IV carbapenems and third generation cephalosporin in conjunction with application of extracorporeal membrane oxygenation to maintain hemodynamic stability.[12]

A number of biomarkers have been identified to help label a specie as hypervirulent, including peg-344, iroB, iucAm prmpA, prmpA2, with an accuracy of >0.95. The string test has also been reported as a variably sensitive test to detect hypervirulent strains but with its low specificity, makes it troublesome in low prevalence areas.[13] Currently, no literature has been published on the markers being used to identify hypervirulent strains of *K. oxytoca*; nor are molecular studies feasible in the clinical setting. The identification of a hypervirulent strain has hence been based on the presentation of a metastatic or toxic disease.

Current guidelines on management of brain abscesses (in general) have described a number of poor prognostic indicators including delayed diagnosis, rapidly progressing disease, coma, multiple lesions, intraventricular rupture, fungal etiology, and extremes of age,[14] unfortunately, the patient had a number of these characteristics, which on top of the inability to maximize medical management, led to the patient's eventual demise. There are currently no guidelines regarding treatment of metastatic *Klebsiella* infection. Susceptibility data has, so far, revealed no difference with respect to the clinical features and antimicrobial susceptibilities between *K. pnuemoniae* and other species of *Klebsiella*.[15,16] Ampicillin/sulbactam, second and third generation cephalosporin, aztreonam, imipenem, aminoglycosides, and quinolones, could all be considered as potentially effective for *K. oxytoca* infection. However, studies on β-lactamases and carbapenemese producing *K. oxytoca* have been reported, most recently that of piperacillin/tazobactam resistant strain recovered from an outbreak in a hospital in Japan.[15] With the emergence of extended-spectrum β-lactam antibiotic resistant *K. oxytoca* infection, decision on antibiotic therapy has become more challenging; with mortality rates ranging between nine to 24%.[16,17]

Conclusion

Community acquired hypervirulent *K. oxytoca* infection has presented an array of problems, namely: a) the low level of suspicion on the part of the health care provider given the current knowledge on its epidemiology, b) the lack of laboratory tests to predict the virulence of the specific infecting strain, as well as one practical enough to be used in the clinical setting, and finally c) the lack of local susceptibility data for individualization of therapy to optimize clinical outcome. Further studies must be done to identify local susceptibility characteristics and molecular markers of *K. oxytoca*. Careful clinical assessment and administration of appropriate antibiotic with the guidance of culture studies are essential to control these infections as well as to prevent further complications.

Ethical considerations

The paper conformed to the Data Privacy Act of 2012 (Republic Act No. 10173) and the principles in the Declaration of Helsinski. In accordance to these, the identities of the patient as well as the attending physicians were remained anonymous. Unfortunately, the patient was not able to give her consent for the publication of her case because she is deceased. Further, no relative could be contacted to serve as proxy. Instead details of the case were not disclosed to prevent identification of the patient.

Disclosure: None to declare

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