Adult intracranial infection caused by an extended-spectrum-beta-lactamase-producing strain of hypervirulent *Klebsiella pneumoniae*: a case report

Junyu Wang[#], Dexiang Xu[#], Binbin Qu, Chuanxin Geng

Department of Pharmacy, The Affiliated Qingdao Central Hospital of Qingdao University, Qingdao, China

[#]These authors contributed equally to this work and should be considered as co-first authors.

Correspondence to: Chuanxin Geng. Department of Pharmacy, The Affiliated Qingdao Central Hospital of Qingdao University, Qingdao 266042, China. Email: gengchuanxin@163.com.

Background: *Klebsiella pneumoniae* is a conditional pathogen related to several infectious diseases. Few studies reported *Klebsiella pneumoniae* meningitis in the Chinese population, guidelines on diagnosis and treatment of *Klebsiella pneumoniae* meningitis should be considered due to its high lethality. Here, we report a case of adult intracranial infection caused by extended-spectrum-beta-lactamase (ESBL)-producing hypervirulent *Klebsiella pneumoniae* (hvKP) in a 65-year-old female, providing new insight for clinical awareness and epidemiological surveillance for ESBL-producing hvKP infection.

Case Description: A 65-year-old female who had a recurrent fever for more than 1 month, and vomiting for 1 week was admitted to our hospital. The computed tomography (CT) results and laboratory results indicated systematic infection, and the blood culture confirmed the infection of *Klebsiella pneumoniae*. A combination of antibiotics including vancomycin, caspofungin, dexamethasone, and posaconazole oral suspension was given to the patient. Further, she exhibited a convulsion with unconsciousness, the CT revealed lacunar infarction and encephalomalacia. The following physical examination showed slight neck resistance, a weak light response of the eye, low muscle tension, suspicious left Babinski sign (+), and right Babinski sign (–). The CT and cerebrospinal fluid (CSF) analyses confirmed the diagnosis of intracranial infection caused by *Klebsiella pneumoniae*. We employed CSF microbial metagenomic next-generation sequencing (mNGS) was employed and the results suggested the high sequence of *Klebsiella pneumoniae* with drug-resistant gene SHV-type beta-lactamases (*blaSHV*). Subsequently, 2 g meropenem every 8 hours (q8h) prolonged for 3 hours was applied to treat intracranial infection, and her body temperature and infectious manifestations were gradually relieved. The CT results represented that pulmonary edema and pleural effusion were gradually dissipated and absorbed. Based on the improvement of clinical manifestations, the patient was discharged from the hospital and a close follow-up was conducted.

Conclusions: An ESBL-producing strain of hvKP could lead to invasive infection such as severe intracranial infection, with a relatively favorable prognosis. The outcome of the disease caused by *Klebsiella pneumoniae* infection is firmly related to the phenotypic features, for instance, virulence factors and antibiotic susceptibility. Due to its high lethality, timely empiric anti-infection therapy and close surveillance are necessary for patients with *Klebsiella pneumoniae* infection in the clinic.

Keywords: Intracranial infection; extended-spectrum-beta-lactamase (ESBL); hypervirulent; metagenomic next-generation sequencing (mNGS); *Klebsiella pneumoniae*; case report

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Introduction

Klebsiella pneumoniae, belonging to the gram-negative aerobic bacteria, is commonly found in communities and healthcare sites. *Klebsiella pneumoniae* is often parasitic in the human respiratory tract, intestinal tract, and biliary tract (1). It is an important conditional pathogen related to several infectious diseases, such as pneumonia, bacteremia, sepsis, meningitis, pyogenic liver abscess, and urinary tract infections. In some severe conditions, immunocompromised patients may even experience life-threatening diseases such as sepsis and purulent meningitis (2). *Klebsiella pneumoniae* represents an infrequent cause of meningitis in South-East Asia and North-East Asia, frequently associated with septic metastatic complications. And the in-hospital mortality rate of patients with *Klebsiella pneumoniae* meningitis is 8.0%, which increases substantially for those older than 45 years (3).

Along with the development of bacterial virulence and the changes in capsular polysaccharides, a new variant of *Klebsiella pneumoniae* has occurred, namely hypervirulent *Klebsiella pneumoniae* (hvKP). The hvKP has unique phenotypic and genotypic characteristics, for instance, high mucus phenotype, special serotype, and carrying special virulence genes (4). It can lead to a higher infectious rate in patients with low immune function, which also manifests with more severe clinical symptoms. It is traditionally considered that there is no overlap of the hvKP genome between high virulence and multi-drug resistance; most hvKPs are sensitive to commonly used antibiotics (5). Therefore, patients with hvKP infection require timely administration of antibiotics.

The most important mechanism of drug resistance in *Klebsiella pneumoniae* is to produce the extended-spectrum-beta-lactamases (ESBLs) (6). The ESBLs are β-lactamases that can hydrolyze penicillins, cephalosporins, and monocyclic amides, it was reported that the detection rate of ESBLs-producing *Klebsiella pneumoniae* was 27.4% in 2015 (7). With the wide application of new antibiotics such as carbapenems, the drug resistance of *Enterobacteriaceae* has increased, and carbapenem-resistant and fully drug-resistant *Klebsiella pneumoniae* have emerged (8). A study has identified that some phenotypes of *Klebsiella pneumoniae* can produce 1 or more β-lactamases; their plasmids often carry aminoglycosides, quinolones, and other antimicrobial resistance genes at the same time (9). Till now, the diagnosis and treatment of intracranial infection caused by an ESBLs-producing *Klebsiella pneumoniae* are remains difficult, corresponding guidelines on empiric treatment should be considered in the management of bacterial meningitis.

Here, we report a case of adult intracranial infection caused by ESBL-producing hvKP in a 65-year-old female, this case highlights to us that the effective and proper identification of these ESBL-producing *Klebsiella pneumonia* is a key step in the rational prevention and treatment for infectious patients. We present the following article in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3805/rc).

Case presentation

A 65-year-old female who had a chief complaint of recurrent fever for more than 1 month, nausea, and vomiting for 1 week was admitted to our hospital. She had no obvious induction of fever, and her highest body temperature was 38 ℃. No obvious clinical signs were found by physical examination. Routine blood test results showed the following: neutrophil count 6.96×10^9/L ↑, monocyte count 0.86×10^9/L ↑, lymphocyte percentage 14.9% ↓, red blood cell count 3.17×10^{12}/L ↓, hemoglobin content 87 g/L ↓, hematocrit 0.28 L/L ↓, average red blood cell hemoglobin concentration 312 g/L ↓, platelet count 363×10^9/L ↑, platelet distribution width 8.3 fl ↓, and C-reactive protein (CRP) 52.01 mg/L ↑. Her blood routine test showed a gradually decreased platelet count, with abnormal infection indicators. Bone puncture showed megakaryocyte maturation disorder, and blood culture indicated *Klebsiella pneumoniae* sepsis.

She was then admitted to the hematology department and diagnosed with "secondary infectious thrombocytopenia, gram-negative bacilli septicemia (*Klebsiella pneumoniae*), liver abscess, bilateral lung inflammation, type 2 diabetes, and hypertension grade 3 (extremely high risk)". She was given vancomycin, caspofungin, dexamethasone, and posaconazole oral suspension for therapy. Liver abscess puncture and drainage treatment were performed with the assistance of the interventional oncology department. The inflammatory indexes tested by laboratory tests decreased significantly after treatment. During this period, light perception disappeared in the left eye, accompanied by eyelid redness and pain, purulent secretion, repeated fever, and left-sided headache. The diagnosis made by the ophthalmology department was as follows: endogenous endophthalmitis (left), orbital cellulitis (left), rubeosis iridis (left), exudative retinal detachment (left), and diabetic retinopathy (right).

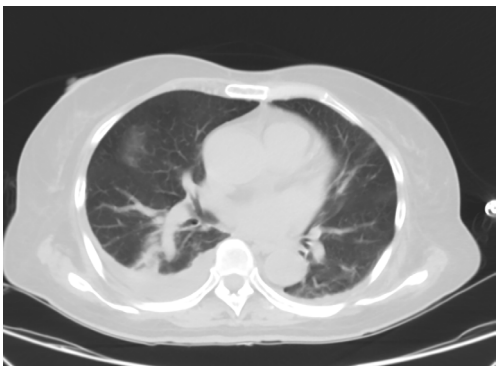

Figure 1 CT examination images on 12 April showed obvious inflammation in both lungs, accompanied by bilateral pleural thickening and effusion, atelectasis in the right inferior lobe. CT, computed tomography.

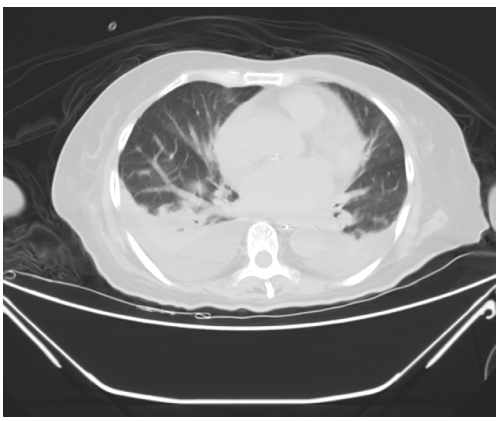

Figure 2 CT examination images on 20 April showed bilateral pleural effusion, the lower lobe of the right lung was insufficiently inflated. CT, computed tomography.

Intravitreal injection with vancomycin and ceftazidime was given 3 times into the left eye, the symptoms were relieved, and the patient's current systemic infection was under control. On 7 April, 2022, the patient was treated with left eyeball enucleation, and she had a fever again after the operation. After the operation, anti-infection medicine including moxifloxacin and sulperazon was administered; however, her temperature elevated again. The computed tomography (CT) examination images performed on 12 April, revealed inflammation of both lungs, pericardial effusion, bilateral pleural thickening and effusion, and atelectasis in right inferior lobe (*Figure 1*); liver cyst and liver abscess, right renal cyst, and myoma of the uterus.

She had a history of hypertension for more than 10 years, with the highest blood pressure of 180/100 mmHg. Oral valsartan was applied to control blood pressure at 140/80 mmHg. She had no special history of other systematic diseases, tuberculosis, infectious hepatitis, or syphilis. She had no history of surgery, blood transfusion, or drug allergy. She was diagnosed as follows: (I) sepsis, (II) secondary thrombocytopenia, (III) liver abscess, (IV) gram-negative bacilli sepsis (*Klebsiella pneumoniae*), (V) infection of lumbar vertebrae, (VI) mesenteric panniculitis, (VII) pelvic effusion, (VIII) pericardial effusion, (IX) suppurative endophthalmitis (left), (X) orbital cellulitis (left), (XI) retinal detachment (left), (XII) choroidal detachment (left), (XIII) type 2 diabetes retinopathy (right), (XIV) cortical senile cataract (right, immature stage), (XV) type 2 diabetes, type 2 diabetes nephropathy stage I, and type 2 diabetic peripheral neuropathy, (XVI) hypertension, grade 3 (extremely high risk), (XVII) hepatic cyst, (XVIII) renal cyst, (XIX) hypoproteinemia, (XX) coronary atherosclerotic heart disease, (XXI) lacunar cerebral infarction, (XXII) moderate anemia, and (XXIII) risk of malnutrition.

On 20 April, the patient experienced a convulsion with unconsciousness, and she was transferred to the respiratory intensive care unit with pharmaceutical care. An emergency CT examination revealed the lacunar infarction and encephalomalacia; bilateral pleural effusion, and the lower lobe of the right lung was insufficiently inflated, which was slightly more advanced than at the previous examination (*Figure 2*). She was in a coma and unresponsive, with uncooperative physical examination, slight neck resistance, a weak light response of the eye, uncooperative physical examination of limb muscle strength, low muscle tension, suspicious left Babinski sign (+), and right Babinski sign (–). The impression was "intracranial infection". Lumbar puncture was performed and the cerebrospinal fluid (CSF) was sent for biochemistry analysis and microbial metagenomic next-generation sequencing (mNGS; IDseq^{TM} Ultra). Biochemistry analysis on 21 April manifested as follows: glucose <1.1 mmol/L ↓, chlorine 108 mmol/L ↓, CSF protein >3,000 mg/L ↑. Microbial mNGS results showed a high sequence of *Klebsiella pneumoniae* with drug-resistant gene SHV-type beta-lactamases (*blaSHV*). We administered 2 g meropenem every 8 hours (q8h) prolonged for 3 h to treat intracranial infection, and the body temperature, blood routine, and CRP were gradually improved. The CT examination on 18 May suggested that pulmonary edema and pleural effusion were gradually dissipated and absorbed (*Figure 3*). The CSF analyses performed on

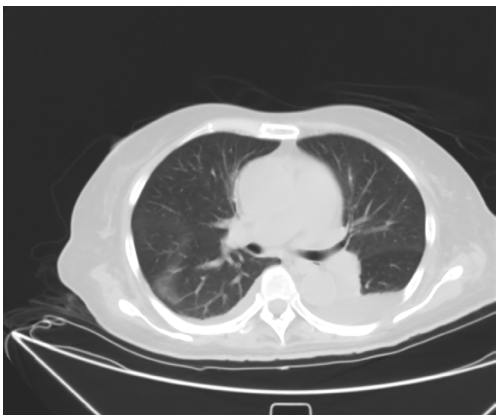

Figure 3 CT examination on 18 May. The results suggested that pulmonary edema and pleural effusion were gradually dissipated and absorbed compared with previous images. CT, computed tomography.

23 May showed the following: chlorine 119 mmol/L ↓, micro amount of proteins 1,107 mg/L ↑, microalbumin 816.3 mg/L ↑, immunoglobulin G 308.5 mg/L ↑, α2-macroglobulin 18.5 mg/L ↑, and β2-microglobulin 2.67 mg/L ↑. Based on the improvement of clinical manifestations, the patient was discharged from the hospital on 31 May and a close follow-up was conducted. The treatment timeline was shown in *Figure 4*.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Klebsiella belongs to the *Enterobacteriaceae*, among which *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Klebsiella ozaenae* are inclined to lead to central system infection, and *Klebsiella pneumoniae* is the most clinically common (10). Here, we have reported an intriguing case of a severe intracranial infection caused by ESBL-producing hvKP in a 65-year-old female. The biochemistry analysis and microbial mNGS of CSF indicated the high sequence of *Klebsiella pneumoniae* with drug-resistant gene *blaSHV*. Subsequently, 2 g meropenem q8h prolonged for 3 hours was applied to treat the intracranial infection. The incidence of *Klebsiella pneumoniae* infection usually develops rapidly with high mortality, herein, we provided this case report of *Klebsiella pneumoniae*-caused intracranial infection in an adult, and relevant literature was reviewed.

In this case, the patient's CSF was examined by mNGS and the results suggested the *Klebsiella pneumoniae* infection with drug-resistant gene *blaSHV*. The *blaSHV* gene is named based on its features of hydrolyzing cefothiophene molecule, which belongs to ESBL. Ojdana *et al.* (11) introduced ESBLs as one of the most well-known resistance mechanisms in gram-negative bacilli. The ESBLs are a group of enzymes that lead to resistance increase in aztreonam, ceftazidime, cefotaxime, related oxyimino-β-lactams, cephalosporins, and penicillins (12). In this case, *blaSHV* was reported as 1 of the 3 main types of ESBLs. Pishtiwan *et al.* (13) found that *blaSHV* accounts for 16.2% in ESBL-producing *E. coli* strains. Bourgeoning studies have confirmed the presence of *blaSHV* in *Klebsiella pneumoniae* infection. Carvalho *et al.* (14) reported that different ESBL variants of CTX-M and SHV-type were detected in *Klebsiella pneumoniae* isolates, in occasions associated with carbapenemase genes. Chaudhry *et al.* (15) found that the highest percentage prevalence of ESBL-producing *Klebsiella pneumoniae* was wastewater in the hospital, and *blaSHV* was found at a percentage prevalence of 6%. Therefore, strict rules and regulations should be adopted at the public- as well as hospital-level to restrict the dissemination of antibiotic resistance from the hospital environment to humans.

Carbapenems are the last defensive line to treat gram-negative bacteria with ESBL production (16). However, evidence of hvKP has been increasingly reported in recent years in China, which poses a great threat to clinical treatment (17,18). In this case, for the patient, who had a recurrent fever for more than 1 month, the CT results and laboratory results indicated the systematic infection, and blood culture confirmed the infection of *Klebsiella pneumoniae*. Although a combination of antibiotics was given, her body temperature remained high, with obvious infectious manifestations and signs detected by laboratory tests and CT examination. Further, she presented with the typical symptoms of intracranial infection, following a physical examination, CT and CSF analyses confirmed the diagnosis of intracranial infection by *Klebsiella pneumoniae*. At first, we speculated that this *Klebsiella pneumoniae* strain may belong to hvKP, which acquires drug resistant genes during the disease development. To confirm our hypothesis,

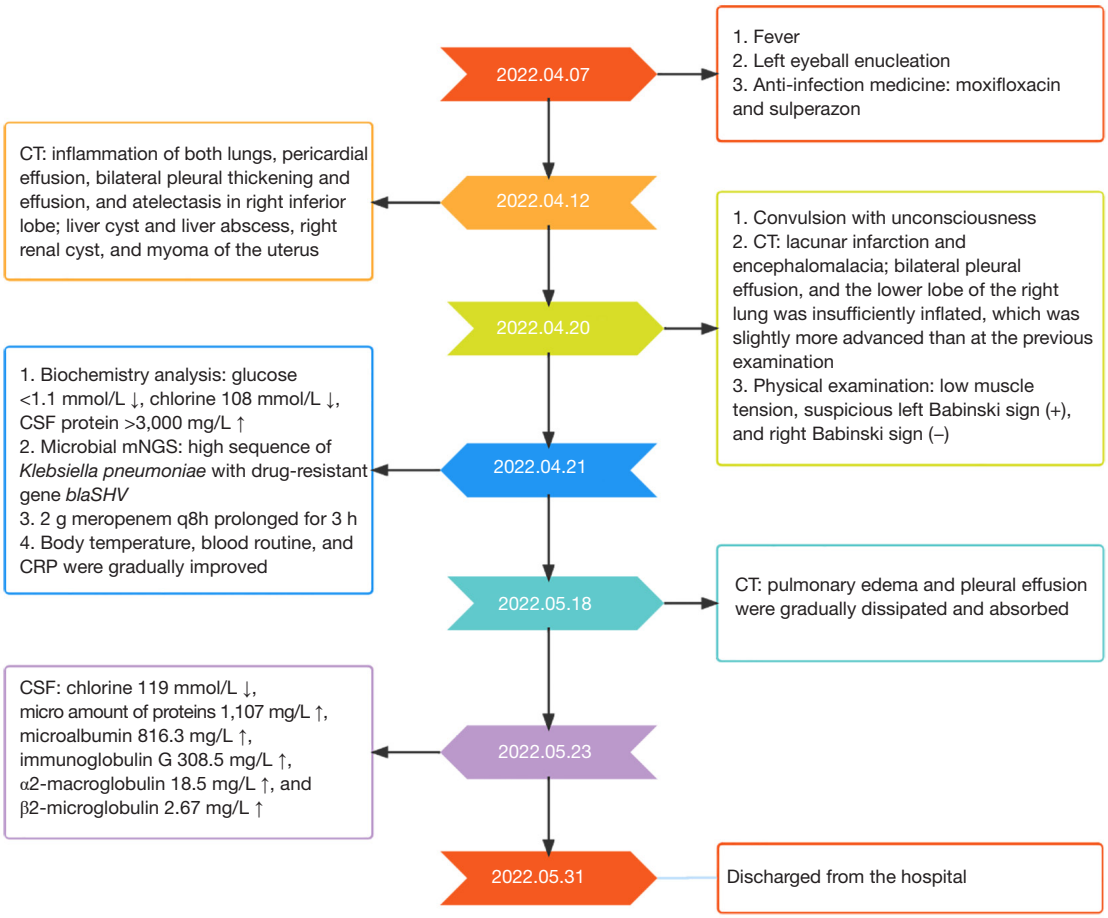

Figure 4 The timeline during the treatment of this patient. CT, computed tomography; CSF, cerebrospinal fluid; mNGS, metagenomic next-generation sequencing; q8h, every 8 hours; CRP, C-reactive protein.

CSF microbial mNGS was employed. Unexpectedly, the mNGS results suggested the high sequence of *Klebsiella pneumoniae* with drug-resistant gene *blaSHV*, thus we deduced that there may be the coexistence of drug resistance genes and high virulence in *Klebsiella pneumoniae* in the present case.

It is well accepted that *Klebsiella pneumoniae* has the potential to develop an increased antimicrobial resistance and virulence. The classic non-virulent strain of ESBL-producing *Klebsiella pneumoniae* is related to some nosocomial infections (19). Some hvKP strains are associated with invasive infection among previously healthy ambulatory patients, and most of them exhibit antimicrobial susceptibility (20). Several cases of infectious diseases caused by *Klebsiella pneumoniae* have been reported, which could produce ESBL worldwide. Khaertynov *et al.* (21) reported the case of a 12-day-old neonate with pyogenic meningitis with poor prognosis, the blood and CSF cultures were positive for *Klebsiella pneumoniae*, producing ESBL. *Klebsiella pneumoniae* isolates were resistant to aminopenicillins and third generation cephalosporins, but were sensitive to imipenem and meropenem.

Here, we report a case of adult intracranial infection caused by ESBL-producing hvKP in a 65-year-old female. Biochemistry analysis and microbial mNGS of CSF indicated the high sequence of *Klebsiella pneumoniae* with drug-resistant gene *blaSHV*. She was treated with 2 g meropenem q8h prolonged for 3 hours, and the manifestations were relieved. This case highlighted that the outcome of the disease caused by *Klebsiella pneumoniae* infection is firmly related to the phenotypic features, for instance, virulence factors and antibiotic susceptibility.

Here, the presence of ESBL-producing hvKP could contribute to a more severe threat to public health, the appropriate management of similar case such as urgent and rational prevention and treatment is needed.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3805/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3805/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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