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CASE REPORT

Otitis Media Progressing to Community-Acquired Meningitis in Diabetic Patients: A Case Report of K2-ST375 hypervirulent *Klebsiella pneumoniae* and Literature Review

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Abstract: Community-acquired *Klebsiella pneumoniae* meningitis (CA-KPM) can rapidly progress to invasive infection in healthy individuals. We present the case of a 54-year-old man with a history of acute suppurative otitis media and uncontrolled type 2 diabetes mellitus (T2DM), who had been treated with oral antibiotics intermittently and irregularly for one month. His symptoms did not improve and continued to worsen, leading to fever and coma. Metagenomic next-generation sequencing (mNGS) of cerebrospinal fluid (CSF) identified *Klebsiella pneumoniae* (KP) after 24 hours in the intensive care unit (ICU). Subsequent CSF culture confirmed a hypervirulent KP (hvKp) strain with capsular genotype K2 and sequence type (ST) 375. Fortunately, the patient made a full recovery with targeted antimicrobial therapy and was discharged. Despite the delayed diagnosis, the outcome was favorable. This case highlights the importance of clinicians, particularly otolaryngologists, maintaining a high index of suspicion for CA-KPM in patients with both otitis media and T2DM, emphasizing the need for timely multidisciplinary consultation.

Keywords: *Klebsiella pneumoniae*, hypervirulent, case report, meningitis, community-acquired

Introduction

Adult community-acquired meningitis (ACAM) is mostly caused by two pathogens: *Streptococcus pneumoniae* and *Neisseria meningitidis*.[1] *Streptococcus pneumoniae* is the primary culprit behind bacterial meningitis, responsible for 25–41% of cases.[2,3] Gram-negative bacilli rarely cause ACAM, most cases occur in newborns or infants.[4] Gram-negative bacilli often lead to nosocomial meningitis, particularly as a consequence of head trauma and cranial surgery.[5,6]*Klebsiella pneumoniae* (Kp) was first identified by Carl Friedländer in 1882 as the pathogenic microorganism causing pneumonia.[7] Hypervirulent Kp (hvKp) is a highly pathogenic variant of classical Kp (cKp), known for causing severe infections even in healthy individuals. HvKp is characterized by enhanced capsule production, siderophore production, and hypermucoviscosity. In the past thirty years, hvKp has gained recognition as a highly pathogenic pathogen, capable of inducing severe, invasive conditions, such as pyogenic liver abscesses, endophthalmitis, meningitis, and necrotizing fasciitis, affecting both healthy and immunocompromised patients. Kp is a critical pathogen in both community-acquired and hospital-acquired meningitis.[8] Previous research has consistently shown Kp to be a leading cause of nosocomial meningitis. Although the incidence of community-acquired *Klebsiella pneumoniae* meningitis (CA-KPM) is relatively low, there has been a global increase in recent years, with the majority still predominantly found in Asia.[9,10]

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CA-KPM poses a diagnostic challenge as it may be the absence of typical clinical symptoms in the initial phase. The challenges in diagnosis may result in an underestimation of the meningitis cases. Accurate and detailed information about pathogens is essential for effective infectious disease management and predicting the patient's prognosis. Metagenomics next-generation sequencing (mNGS) can directly detect pathogens and provide comprehensive details about their strains. In this report, we retrospectively analyzed a Chinese male diagnosed with CA-KPM using mNGS and cerebrospinal fluid (CSF) culture. The mNGS identified the Kp strain as K2 serotype, sequence type (ST) 380, which had not been fully explored in CA-KPM cases.

Case Presentation

A 54-year-old Chinese man was admitted to the emergency room with a three-day history of diarrhea and vomiting, followed by a one-day history of fever and coma. When he was admitted to the emergency department (ED), his blood sugar level was high, and a rapid blood ketone test was positive. In the preceding month, the patient frequently visited the otolaryngology outpatient department due to recurrent episodes of acute suppurative otitis media in the right ear. Due to the lack of microbiological documentation, he was intermittently treated with oral cephalosporin antibiotics to manage the infection. The patient was diagnosed with type 2 diabetes mellitus (T2DM) 10 years ago, and his blood sugar has remained uncontrolled for the last three months.

On admission, the patient had a Glasgow coma scale (GCS) of E2 + V3 +M4. He had a high-grade fever of 39.0, tachycardia of 123 beats/min, blood pressure of 89/54 mmHg, and oxygen saturation of 97% on ambient air. Neurological examination revealed motor or sensory deficits in both his upper and lower extremities, along with neck stiffness and absent reflexes. The non-contrast computer tomography (CT) scan of the head showed no abnormalities, with the only finding being chronic otitis media in the right ear (Figure 1A). CT-scan of the chest and abdomen were normal, with no pneumonia or liver abscess. Laboratory testing revealed neutrophilic leukocytosis, elevated levels of C-reactive protein (1897 mg/dL; reference: <1.0 mg/dL), procalcitonin (5.03 ng/mL; reference: <0.1ng/mL), fasting blood glucose (424.8 mg/dL; reference: <110 mg/dL), HbA1c (8.4%; reference: <6.0%), and abnormal blood ketone bodies (4.5mmol/L, reference: <0.30 mmol/L). Arterial blood gas results (ABG) results showed as follows (on 6L/min oxygen via nasal cannula): pH of 7.037, PaCO2: 45 mmHg, PaO2: 111 mmHg, HCO3-: 12.1 mmol/L, base excess: −18.5 mmol/L, lactic acid: 0.8 mmol/L and other blood tests were normal. The emergency physician then performed a lumbar puncture (LP). CSF was mucopurulent and chyliform, and CSF pressure was 300mmH2O, with the following abnormalities: glucose was 209 mg/dL (blood glucose: 540.0mg/dL at the same time), protein 23.62 g/L, and 149146 white blood cells (WBC)/mm3, (73% of polymorphonuclear (PMN) cells) (Table 1). A Gram-negative bacilli was observed on direct microscopy of CSF. Immediately after LP, an intravenous prolonged infusion of meropenem (2.0 g, q8h, 2–4 hours) was started and the patient was intubated and transferred to the intensive care unit (ICU). The bacterial

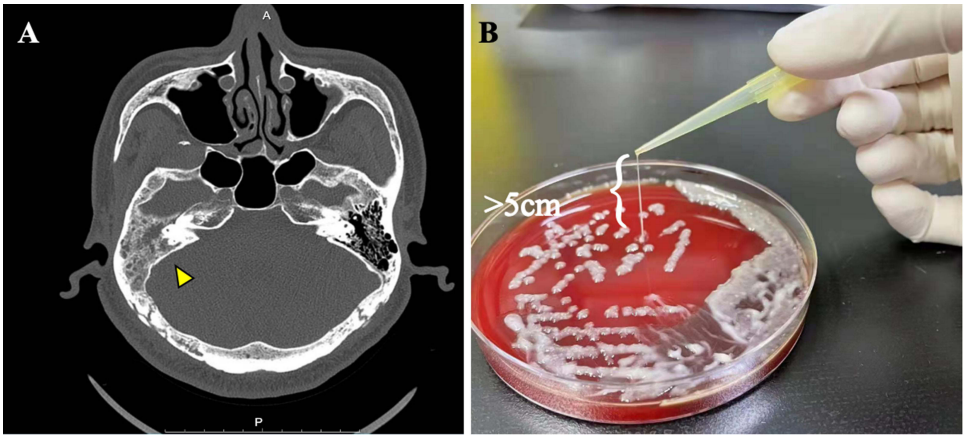

Figure 1 (**A**) The non-contrast CT scan of the head chronic otitis media of the right ear; (**B**) String test. Positive of string test of *Kp* strain. In this case, the string reached more than a length of 5 mm, confirming the hyperviscosity of the pathogen.

Table 1 CSF Analysis Results for a Patient with CA-KPM

CSF Data	Day of Admission	1 week	2 weeks	3 weeks
CSF appearance	Cloudy	Cloudy and purulent necrotic material	Semi-transparent and purulent necrotic material	Transparent and clear
CSF pressure (reference: 70–180 mmH_2O)	> the maximum measurable limit	30	15	8
Protein (reference:0.15–0.5g/L)	23.62	11.48	9.04	1.53
Glucose (reference:2.2–3.9mg/dL)	209	0	3.06	95.58
Chlorine (reference:120–130mmol/L)	117.4	131.6	132.5	118.2
WBC/mm^3(reference:0–8)	149,146	93,470	4160	43
Percentage of PMN cells (%)	73	86	86	33

culture of the right ear swab and rectal swab were negative. We have performed the analysis of meropenem concentrations in serum and CSF and routine therapeutic drug monitoring (TDM). According to the guidelines for healthcare-associated ventriculitis and meningitis by the Infectious Diseases Society of America (IDSA), CSF concentrations aim at 10 to 20 times the pathogen minimum inhibitory concentration (MIC).[11] The dose remained unchanged on day 3, median serum penetration was 11.82 mg/L, and median CSF penetration was 10.98 mg/L.

Metagenomics next-generation sequencing (mNGS) of the CSF identified Kp (specific sequence reads number (SSRN)=637222) 24 hours after the LP. After five days, the CSF culture yielded hypermucoviscous Kp with a wild-type susceptibility profile (MIC of meropenem ≤0.5 mg/L, MIC of ceftriaxone ≤0.25 mg/L). The string test is positive (Figure 1B). A lumbar subarachnoid drain was inserted for the continuous drainage of purulent cerebrospinal fluid, to alleviate symptoms of increased intracranial pressure. His CSF was scheduled for biweekly laboratory analysis and culture. CSF culture remained negative during meropenem was prescribed. Meropenem was continued for 6 days and changed to ceftriaxone 2 g every 12 h for the next 30 days. Repeat CSF with improved parameters in 3 weeks after admission: CSF was clear, glucose 95.58 mg/dL (blood glucose:180.0 mg/dL at the same time), protein 1.53 g/L, 43 WBC/mm3 (33% of PMN cells) (Table 1). Figure 2 shows the transformation of CSF from cloudy to clear.

The CSF culture taken at admission identified Kp, susceptible to commonly used antibiotics but intrinsically resistant to ampicillin. For detailed characterization, mNGS of the Kp strain was performed, focusing on capsular genotyping, virulence factors, and multilocus sequence typing (MLST). This analysis revealed that the isolate was a serotype K2, sequence type (ST) 375 strain, equipped with virulence genes, such as rmpA2, iroB, iroN, iucA, iutA, and entB. The RmpA2 gene is a regulatory gene that enhances capsule production and serves as the regulator of the mucoid phenotype; it is associated with the hypermucoviscous phenotype. The iroB and iroN genes are components of the iroBCDEN gene cluster, which are responsible for the biosynthesis of the siderophore salmochelins. The iucA and iutA genes, forming part of the iucABCD-iutA gene cluster, are essential for the biosynthesis of the siderophore aerobactin. The entB gene is responsible for the production of enterobactin. The strain was also found to carry the wzi-72 gene sequences, which have been specifically identified in strains of the capsular serotype K2, another significant virulence factor in Kp.

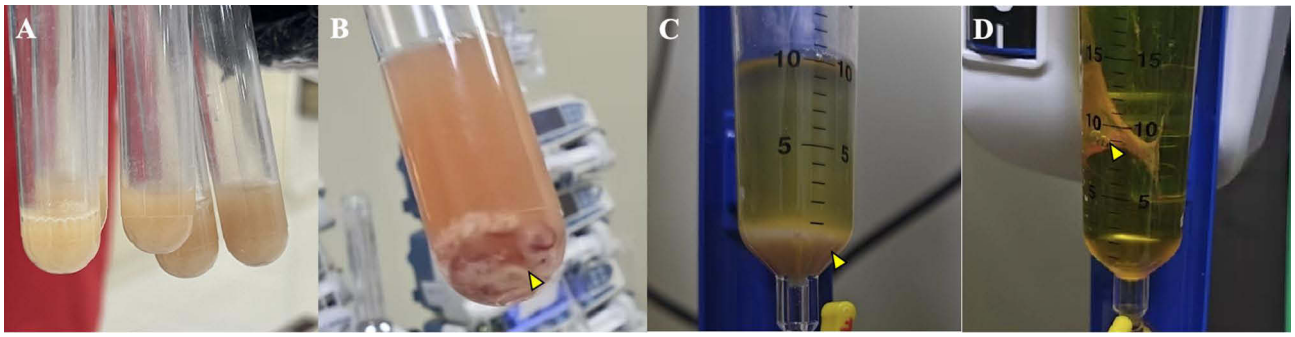

Figure 2 Transformation of CSF from cloudy to clear, with the yellow arrow indicating necrotic material. (**A**) Day of admission; (**B**) 1 week after admission; (**C**) 2 weeks after admission; (**D**) 3 weeks after admission.

The patient gradually regained consciousness. The lumbar subarachnoid drain was removed on the 23rd day after admission. He was successfully extubated on the 28th day. On follow-up Magnetic resonance imaging (MRI), reveals multiple abnormal signal areas in the right frontal lobe, right basal ganglia, and left parieto-occipital lobe. The findings include localized roughness on the surface of both cerebral hemispheres and suspected signal irregularities, which may align with infectious lesions. It appears that the intracranial infection has extended from the cerebrospinal fluid into the brain tissue. Given the absence of any discomfort in the patient, pinpointing the exact timing of the brain tissue's involvement is challenging. These MRI findings are likely associated with residual lesions from a previous acute phase of purulent meningitis. He was discharged to a rehabilitation hospital for ongoing treatment on the 50th day after admission. At the time of discharge, he was alert but still experienced a decrease in right ear hearing and reduced motor function in all four limbs. Telephone follow-up indicated the patient was progressing well (Figure 3).

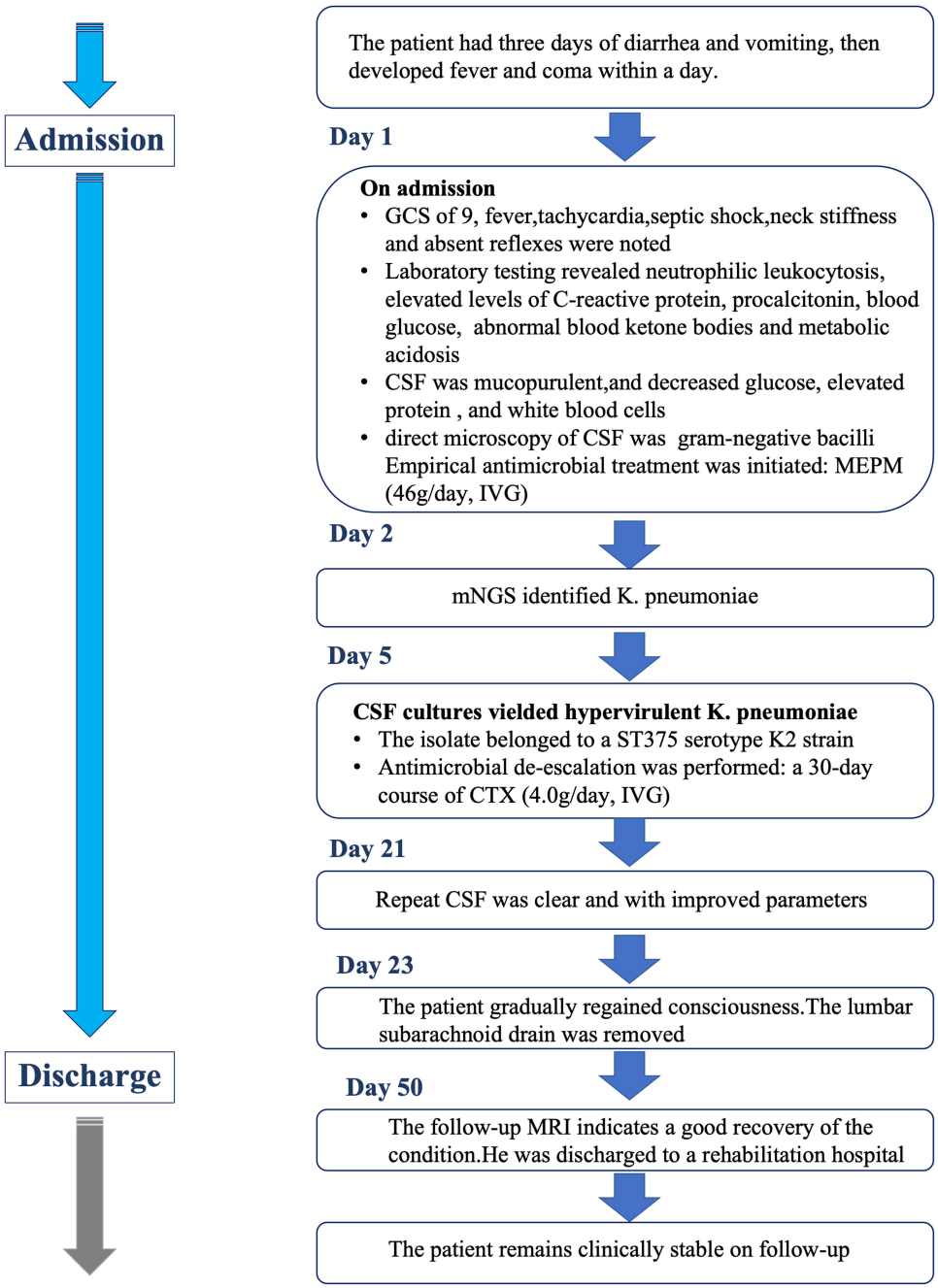

Figure 3 The timeline for the case presentation and the patient's clinical progression.

Table 2 Case of Reports on Community-Acquired Meningitis Caused by Hypervirulent Kp Strains

	Country	Case	Age	Sex	Underlying Diseases	Clonal Group/ ST	Serotype	Virulence Genes	Duration of Antimicrobial Therapy	Outcomes
Chang (2023)	China	1	68	Male	T2DM	–	–	–	42 day	Survived
Li (2022)	China	1	69	Female	T2DM, tuberculosis	–	–	–	14 days	Died
E. T. S. En (2023)	Malaysia	1	10	Female	Right ear pus	ST65	K2	rmpA, rmpA2, iucA, peg344	–	Died
Zhang (2022)	China	1	1 month	Female	No mention	ST86	K2	peg-344, iroB, rmpA	20 days	Survived
Liu (2022)	China	1	55	Male	T2DM	-	-	-	50 days	Survived
A. R. Nayak (2022)	India	1	48	Male	T2DM, chronic alcoholism	-	-	-	42 day	Survived
Zhao (2021)	China	1	64	Female	No mention	-	-	-	63 days	Survived
Zeng (2021)	China	1	59	Female	No mention	-	-	-	29 days	Survived
Wang (2019)	China	1	69	Male	No mention	-	K1	magA	23 days-3 months	Survived
T. Hosoda (2019)	Japan	1	71	Male	Hepatitis B virus and HTLV-1 carrier status, chronic alcoholism	ST 23	K1	magA, rmpA, iutA fimH, aerobactin, iroN	7 days	Died
M. Hentzien (2016)	France	1	56	Male	Tobacco use, chronic alcoholism	ST 380	K2	rmpA	68 days	Died
B. Melot (2016)	Caribbean	1	55	Male	Obstructive sleep apnea, chronic alcoholism	CG86/ ST86	K2	rmpA,rmpA2, iroBCDN, iucABCDiutA, kvgAS, mrkABCDFHIJ, wzi-2,wzc-2	21 days	Survived
Y. Iwasaki (2016)	Japan	1	72	Male	T2DM,hypertension, cerebral hemorrhage	ST 29	K54	rmpA, terA, iroN, iucA	40 days	Survived
K. Takahashi (2016)	Japan	1	89	Male	No mention	-	-	magA, rmpA	15 days	Died
H. I. Shih (2006)	Taiwan		58	Male	T2DM, liver cirrhosis	-	-	-	2 days	Died

Discussion

We report a case of community-acquired meningitis caused by a K2-ST375 hypervirulent strain of Kp in mainland China. The patient started with acute diarrhea and gradually developed into altered consciousness, posing a challenge in diagnosing purulent meningitis in the ED. He was then effectively managed with targeted antimicrobial treatment and CSF drainage. Our case highlights several important clinical insights.

Firstly, our case involved a patient with CA-KPM caused by K2-ST375 hypervirulent strain. To understand the characteristics and epidemiological trends associated with CA-KPM, we conducted a comprehensive review of existing case reports (Table 2). The literature search, restricted to English language publications, was conducted using the PubMed electronic database, covering the period from January 1, 2009, to February 25, 2024. The search was used using the following terms: "Klebsiella pneumoniae"(Mesh) and "Meningitis"(Mesh) and "hypervirulent"(tiab). A total of 15 cases were included.[9,10,12–24] Generally, CA-KPM is rare and exhibits geographical variations, with a higher incidence in Asian populations.[25] There was a lack of research reporting on specific incidence rate of CA-KPM and only isolated case reports published. CA-KPM can appear as the initial infection or as a consequence of metastatic spread. In settings without neurosurgical procedures or head trauma, Kp has risen as a key contributor to community-acquired meningitis in Asia.[25] CA-KPM is more prevalent in males and typically occurs in young and middle-aged individuals, with an average age of fifty-one.[26,27] The study of Fang et al indicates that the K1 genotype of Kp is responsible for 81% of central nervous system complications arising from pyogenic liver abscesses.[28] The causative pathogen in our patient has been

identified as the hvKp strain with the capsular genotype K2-ST375, which was not previously described in research on CA-KPM. Several case reports have documented instances of genotype K2.[9,12,21,23] Within the K2 serotype, sequence types like ST380, ST86, and ST375 are increasingly identified in severe community-acquired infections.[29] Virulence genes such as rmpA2, iroB, iroN, iucA, iutA, and entB, identified through molecular analysis, are biomarkers for hvKp.[30,31] Moreover, evidence suggests that identifying two particular virulence plasmids can signify hvKp: the pLVPK plasmid (219-kb), which contains genes linked to hypervirulence, such as iuc, iro, rmpA, and rmpA2; and the Kp52.145 Plasmid II (pKpST66-2) (121-kb), harboring genes iuc2, iro2, and rmpA. The outcomes for CA-KPM are poorer compared to those for non-CA-KPM, characterized by increased incidences of in-hospital deaths, 28-day mortality rates, extrameningeal infections, and septic shock.[32] The comparative study between spontaneous meningitis (SM) and postsurgical meningitis (PSTM) caused by Kp revealed that SM cases were more severe than PSTM ones, marked by a higher frequency of septic shock ($p = 0.004$) and elevated in-hospital mortality rates ($p = 0.004$).[33] T2DM was the predominant underlying disease associated with KP infection, observed in 48.1% to 59.0% of cases, with liver cirrhosis next, affecting 14.3% to 22.2% of individuals, and 14.3% of the patients had a history of alcoholism.[27,32,34]

CA-KPM diagnosis involves evaluating clinical symptoms (fever, stiff neck, altered consciousness, possible seizures, etc)., CSF analysis (increased WBCs, proteins, low glucose, etc)., microbiological diagnosis (positive CSF culture for Kp, possible positive blood cultures for Kp), and imaging examination (head CT or MRI, etc). Almost every CA-KPM patient reported symptoms of headaches, fever, and/or neck stiffness. 66.7% of the patients exhibited disturbances in consciousness, and 14.5% experienced seizures.[27] However, realizing an accurate diagnosis for CA-KPM is by no means a straightforward task. The diagnosis process for this patient notably highlighted the crucial importance of differentiating among various reasons for altered consciousness. CA-KPM is often misdiagnosed as a stroke or diabetic ketoacidosis (DKA), leading to time delay in the accurate diagnosis and proper treatment. Our patient was admitted with coma and elevated blood sugar levels, along with the presence of blood ketone bodies, which initially led to a diagnosis of DKA. Further thorough physical assessments and an LP subsequently confirmed a diagnosis of meningitis. This case underscores the significance of quickly recognizing CA-KPM in individuals with T2DM in the ED.

Secondly, It's important to note that meningitis caused by Gram-negative bacilli typically results in high fatality rates, ranging from 40% to 80%, and survivors often suffer from various complications.[35] Insufficient understanding and diverse clinical manifestations of this condition often lead to its underrecognition by medical practitioners, especially those in primary care settings. Delayed initiation of effective antimicrobial therapy can result in elevated mortality rates in severe cases. Previous research consistently shows that delayed antimicrobial treatment adversely affects mortality rates and can result in persistent neurological deficits.[36,37] Traditional microbial cultures are the standard for identifying pathogens, but they have low sensitivity (10–50%) and require 24–72 hours for results.[38] Molecular tests such as multiplex real-time polymerase chain reaction (PCR),[39] mNGS,[40] and droplet digital PCR (ddPCR)[41] can rapidly detect pathogens directly from blood. Studies have shown that ddPCR and mNGS enhance the diagnosis of bloodstream and neurological infections, providing valuable information for guiding treatment decisions. In the case of MDR Kp, precision treatment strategies rely on clinical microbiological techniques to determine the MIC, rapidly identify the carbapenemase genotype of Kp isolates, and perform antimicrobial synergy testing to select the most appropriate treatment options.[42] Identification of the capsular genotype, sequence types, and virulence factors are all crucial, given their association with the heightened pathogenicity of hvKp. A number of widely-used detection methods exist, among which are biotyping, serotyping (including capsule typing), phage typing, and diverse molecular typing techniques.[43,44] In our case, the mNGS testing of CSF was confirmed as CA-KPM within 24 hours. K2-ST375 hypervirulent strain of Kp and virulence genes were identified by mNGS of the strain.

Thirdly, meningitis was effectively treated with targeted antimicrobial therapy. The success of antimicrobial treatment hinges on antibiotics reaching and sustaining effective levels at the infection site, especially critical for virulent pathogens like the K2-ST375 Kp strain. Using antibiotics that penetrate the CSF to optimize bactericidal efficacy, based on the pharmacodynamic characteristics of the antimicrobial agents. Tiede et al proposed an individualized dosing strategy, monitoring serum and CSF concentrations of meropenem.[45] This TDM-guided dose optimization strategy seems to be an effective method for achieving adequate CSF concentrations in patients with ventriculitis. Their study retrospectively assessed the serum and CSF concentrations in ventriculitis patients under continuous infusion and routine

TDM, aiming for meropenem serum levels of 20–30 mg/L, with serum-to-CSF ratios for meropenem between 5% and 9%. In our case, the median concentration of CSF was 10.98 mg/L, with the MIC for meropenem being ≤0.5 mg/L. According to the IDSA guidelines, we targeted the CSF concentration to be 10 to 20 times higher than the MIC of the pathogen. Although this result differs from previous studies, it has been sufficient to achieve the goal of effective bactericidal efficacy. The duration of antibiotic treatment varies based on the causative pathogen. IDSA guidelines recommend an optimal antimicrobial therapy duration of 10 to 14 days, which may be extended to 21 days in severe cases.[11] In our case, the patient received meropenem treatment for 6 days, followed by a 30-day course of ceftriaxone.

However, our case illustrated one clinical challenge associated with CA-KPM. The challenge concerned that the precise pathway through which hvKp gains entry remains unidentified. Recent or current occurrences of otitis media might serve as pathways for pathogen entry. However, hvKp is commonly associated with oropharyngeal and colonic colonization, where colonization on the skin and mucous membranes are transient.[46] HvKp-related community-acquired central nervous system infection after acute otitis media is increasingly being reported.[21,47] Emily Tan Sheau En et al documented a case where a 10-year-old child developed a cerebral abscess following otitis media, attributed to hvKp. An otoendoscopic examination of the child's right ear showed a pulsating purulent discharge and a tympanic membrane that was inflamed and had a central perforation. Cultures from surgical pus and blood showed Kp, but a bacterial culture from the purulent discharge of the right ear yielded no positive results.[21] In another case reported by Sun et al, a 55-year-old woman with purulent discharge from her right ear developed a fever and headache, eventually becoming unconscious. Kp was found in cultures from both her CSF and blood.[47] In our case, cultures from both the right ear and rectal swabs were negative, leaving the bacterial entry route unclear. We hypothesize the infection may have stemmed from the right middle ear, indicating a direct route for Kp entry. This suggests Kp might have spread from an initial infection or colonization site to the central nervous system. However, our case had inconsistencies; over a month of otorhinolaryngology outpatient clinic visits, the patient's intact eardrum provided no indication for drainage. Moreover, repeated ear swabs showed no Kp infection or colonization, casting doubt on direct CNS invasion from the ear. Alternatively, the meningitis might have arisen from bacteria spreading through the bloodstream instead of directly from the infection site. Although the specific pathogenesis remains uncertain, the presence of otitis media and T2DM could have been risk factors for meningitis.

In summary, CA-KPM is an uncommon condition. When otitis media and T2DM coexist, they should be considered probable risk factors for central nervous system infections. Employing appropriate antibiotics, TDM-guided dosing, and abscess drainage seems to be an effective treatment strategy. Additionally, mNGS shows promise as a detection method for such cases. Reporting this case aims to increase awareness of this rare disease and contribute to the advancement of knowledge regarding its pathogenesis and management.

Abbreviations

Kp, *Klebsiella pneumoniae*; hvKp, hypervirulent *Klebsiella pneumoniae*; cKp, classical *Klebsiella pneumoniae*; ST, sequence type; CA-KPM, community-acquired *Klebsiella pneumoniae* meningitis; mNGS, metagenomics next-generation sequencing; CSF, cerebrospinal fluid; AST, antimicrobial susceptibility test; GCS, Glasgow coma scale; CT, computer tomography; ABG, arterial blood gas results; LP, lumbar puncture; WBC, white blood cells; PMN, polymorphonuclear; ICU, intensive care unit; TDM, therapeutic drug monitoring; IDSA, the Infectious Diseases Society of America; MLST, multilocus sequence typing; MRI, Magnetic resonance imaging; SM, spontaneous meningitis: PSTM, postsurgical meningitis; T2DM, type-2 diabetes mellitus; DKA, diabetic ketoacidosis; ED, emergency department; BC, blood cultures; PCR, polymerase chain reaction; ddPCR, droplet digital polymerase chain reaction.

Ethics Statement and Patient Consent

All procedures involving human participants complied with the ethical standards set by the institutional and/or national research committees, as well as the 1964 helsinki Declaration and its later amendments or comparable ethical guidelines. This study received approval from the Ethics Committee of Shanghai General Hospital, Nanjing Medical University, Shanghai Jiao Tong University School of Medicine (Approval No. 20240403102009477). The patient provided informed consent for the publication of the case, and both Shanghai General Hospital and the patient agreed to disclose the case details.

Consent for Publication

Written Informed consent statements were obtained from our male participant for publication of identifiable information/images in open access journal.

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This case report was prepared following the CARE Guidelines.

Author Contributions

All authors made significant contributions to the work reported, whether in conception, study design, execution, data acquisition, analysis and interpretation. Shanshan Jin and Hui Xie participated in drafting, revising, or critically reviewing the article. Ruilan Wang gave final approval of the version to be published and agreed to be accountable for all aspects of the work. All authors read and approved the final version and have agreed on the journal to which the article has been submitted.

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Disclosure

The authors declare no competing interests.

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