

Report of a Fatal Purulent Pericarditis Case Caused by ST11-K64 Carbapenem-Resistant Hypervirulent *Klebsiella pneumoniae*

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Abstract: The report describes a 44-year-old female patient who died of the rare acute purulent pericarditis caused by *Klebsiella pneumoniae* (KP). The genomic analysis revealed an extensively drug-resistant ST11-K64 KP strain from five isolates (blood cultures, urine, ascites, pericardial effusion, and sputum). Several high virulence (hv) and carbapenem-resistant (CR) genes were identified in the pericardial effuse isolate. The isolates showed low resistance to healthy human serum. This study highlights the potential lethality of CR-hvKP infections in patients suffering from underlying comorbidities such as diabetes mellitus and chronic ailments.

Keywords: purulent pericarditis, *Klebsiella pneumoniae*, carbapenem-resistance, hypervirulence, ST11, K64

Introduction

Purulent pericarditis is a bacterial infection in the pericardium with gross or microscopic purulence, usually resulting from thoracic trauma, contagious spread of pathogens or hematogenous dissemination.¹ Purulent pericarditis more frequently occurs in populations with compromised immune function or other predisposing factors such as diabetes and drug or alcohol abuse.² It is a rare disease but has a very poor prognosis, requiring life-saving early diagnosis and effective treatment.² Acute purulent pericarditis can rapidly progress into cardiac tamponade, systemic toxicity and cardiac diastolic dysfunction that lead to almost 100% mortality if left untreated and 40% in treated patients.³ The sources of the infection are often non-cardiac but via systemic dissemination from a primary pulmonary or abdominal infection. In recent years, the ascendancy of pathogens causing purulent pericarditis tends to drift from the Gram-positive bacteria such as *Streptococcus pneumoniae* and *Staphylococcus aureus*,¹ to Gram-negative bacteria such as *Proteus*, *Escherichia coli*, *Pseudomonas*, and in rare cases *Haemophilus influenzae*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* (KP),^{2,4-6} a phenomenon that can be attributed to the extensive use of broad-spectrum antimicrobials.⁷

Klebsiella pneumoniae (KP) is an *Enterobacteriaceae* that causes opportunistic infection with community or nosocomial acquirement. According to the types and amount of the mucoid polysaccharide capsule produced, they are characterised into classic KP (cKP) and hypermucoviscous KP (hmKP), the latter often referred to as hypervirulent KP (hvKP) due to its metastatic pathogenicity.⁸ The sequence type (ST) and the capsular antigen (K), as well as other virulence factors, including the extracapsular polysaccharide synthesis regulator genes, the ferric iron uptake system genes and the fimbriae expression genes, are used to classify a range of virulent KP lineages.^{9,10} hvKP is mostly implicated in pyogenic liver abscesses, septicaemia, pneumonia, cystitis, surgical wound infection, endophthalmitis, endocarditis and urinary tract infections.¹¹ The acquisition, exchange, accumulation and convergence of plasmids or transposons coding for advanced virulence and multi-drug resistance of hvKP pose an urgent challenge for clinicians, as

there are no evaluated treatment solutions. Such that the carbapenem-resistant hvKP (CR-hvKP) infection is considered a serious public health threat in Southeast Asia and beyond.^{10,12,13}

Purulent pericarditis caused by KP has been scarcely documented.¹⁴ One report described a positive outcome of a 67-year-old man treated with surgical pericardiectomy and intradiaphragmatic abscess draining, but the virulence and genetic details of the KP strain were not determined.¹⁵ In another report, a capsule genotype K1 hvKP was detected in the isolates of a 43-year-old man with diabetes mellitus and alcoholism. Despite the presence of the virulence-attributing genes, the patient responded well to cefazolin, ceftriaxone and ciprofloxacin and was discharged after the treatment.⁶

We present here the clinical and microbiological findings of a 44-year-old female diabetic patient who developed purulent pericarditis caused by ST11-K64 CR-hvKP infection and died soon after the drainage surgery.

Case Presentation

A 44-year-old woman was admitted to the emergency department of the affiliated hospital of Guizhou Medical University, with complaints of coughing, vomiting, tightness in the chest, shortness of breath, abdominal pain, chills and fevers in the morning and at night that had persisted for half a month and worsened over the past three days. She was subsequently hospitalized into nephrology department with diagnosis of chronic renal failure (CRF). The patient had a medical history of type 2 diabetes mellitus and had been treated for CRF during the last two years. She was taking Euthyrox for treatment of hypothyroidism converted from hyperthyroidism that was diagnosed 20 years ago. Her surgical traumas included caesarean section and inferior vena cava filter placement for venous thrombosis. The physical examination the next day revealed moist rales in both lungs and serum measurement found neutrophilic leukocytosis (WBC count $11.14 \times 10^9/L$ with 96.40% neutrophils), high interleukin-6 (IL-6, 251.20 pg/mL) and procalcitonin (PCT, 100 ng/L). Ceftizoxime was administrated for anti-infection treatment, which was replaced by meropenem after microbial detection of *Klebsiella pneumoniae* from the blood and urine isolates. The patient was discharged after 23 days of treatment when the acute symptoms disappeared and serum parameters returned to normal.

Twelve days later, the patient was re-admitted into the emergency department with a complaint of >10 hours of diarrhoea and >3 hours of impaired consciousness. Soon the patient was sent to the intensive care unit (ICU) due to her condition deteriorating into severe consciousness disorders. The vital signs and physical parameters on admission were the following: body temperature 37.2°C, hypotensive blood pressure 84/47 mmHg, heavy and moist rales in both lungs audible through auscultation, no abnormal bulge/depression or pulsation in the precordial area, no obvious pathological murmur heard by auscultation in all the cardiac valve areas and no oedema in the lower extremities. Laboratory analysis indicated neutrophilic leukocytosis (WBC count $35.22 \times 10^9/L$ with 96.80% neutrophils) and suspicion of sepsis (interleukin-6 5000 pg/mL and PCT higher than 100 ng/L in serum). Computed tomography (CT) of the chest showed a large pleural effusion and abdominal effusion.

The emergency treatments included phlegm removal, sedation, analgesia, vasoactive drugs, anti-inflammation, and anti-infection drug imipenem. A closed drainage of the right thoracic cavity was performed to improve the right pneumothorax. The patient had to be subsequently submitted to orotracheal intubation and an invasive ventilator due to severe hypoxia. Despite all these treatments, her general condition deteriorated. A cardiac ultrasound exam revealed a significantly enlarging pericardial effusion (Figure 1).

Pericardiocentesis drainage was immediately employed, and 150 mL of purulent liquid was withdrawn. Bacterial identification and drug sensitivity test were conducted using MicroScan WalkAway 96 plus automatic analysis system. The drug susceptibility results were verified later by broth microdilution method. A *Klebsiella pneumoniae* strain was confirmed and cultured from the pericardial effusion, which was resistant to multiple antibiotics, especially carbapenems (Table 1). Therefore, the patient was diagnosed with purulent pericarditis caused by CR-KP. CR-KP were also detected in the patient's blood, ascites, and urine.

Within one to two hours after the pericardiocentesis drainage, the patient's heart rate gradually dropped to 40 bpm. The patient failed to regain consciousness despite active resuscitation (ACDCRP) and eventually died, likely from multiorgan failure associated with sustained septic shock.

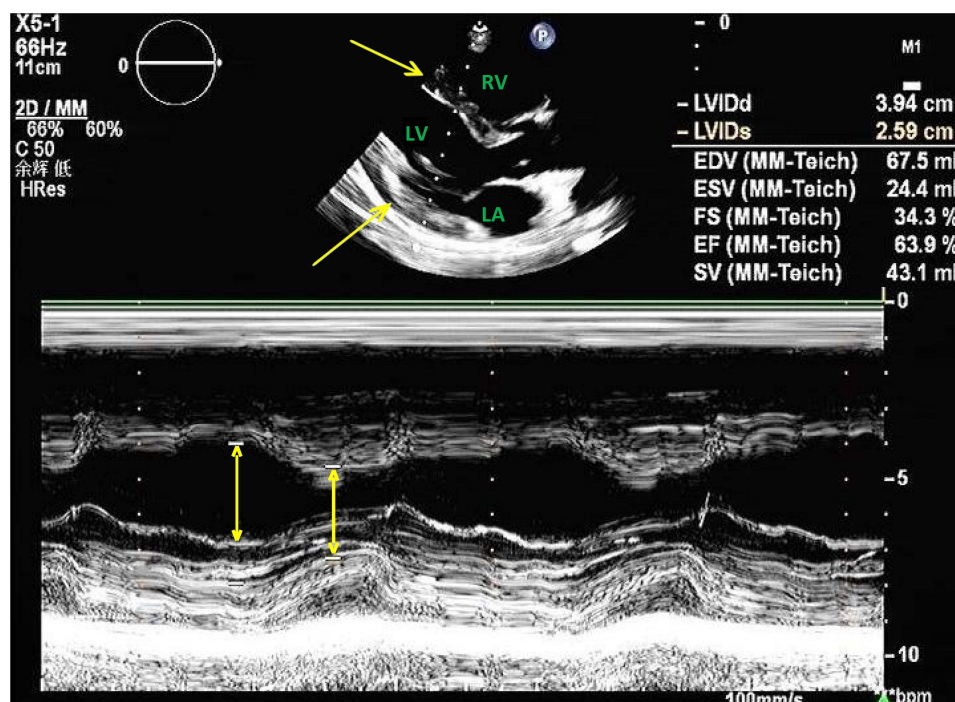


Figure 1 A 2D (top) and M-mode (bottom) imaging of parasternal long-axis echocardiogram showing pericardial tamponade. Bright yellow arrows show dark echo-free signal from pericardial fluid with left ventricular contraction in both end-diastolic and end-systolic.

Abbreviations: RV, right ventricle; LV, left ventricle; LA, left atrium.

Microbiological and Molecular Characterization

Five isolates (blood cultures, urine, ascites, pericardial effusion, and sputum) collected from this patient were positive for ST11 *Klebsiella pneumoniae*, confirmed by PCR screening and DNA sequencing analysis of the seven house-keeping genes of KB (*rpoB*, *phoE*, *gapA*, *infB*, *mdh*, *tonB*, and *pgi*) according to the Institut Pasteur Multilocus Sequence Typing (MLST) databases (<https://bigsd.b.pasteur.fr/klebsiella/>). Using the primers described previously for PCR,¹⁶ the capsular

Table 1 Results of Antimicrobial Susceptibility Testing (Broth Microdilution)

Antibiotic	MIC (µg/mL)	Susceptibility
Cefotaxime	>32	R
Cefoxitin	>16	R
Cefazolin	>16	R
Ciprofloxacin	>2	R
Cefepime	>16	R
Cefuroxime	>16	R
Gentamicin	>8	R
Ertapenem	>4	R
Imipenem	>8	R
Meropenem	>8	R
Levofloxacin	>4	R
Piperacillin/tazobactam	>64	R
Tigecycline	≤2	S
Polymyxin B	I	S

Notes: Interpretative results are reported according to CLSI document M100 (Performance Standards for Antimicrobial Susceptibility Testing, 31st Edition 2021).

Abbreviations: MIC, minimum inhibitory concentration of the antibiotic; R, resistant, S, sensitive.

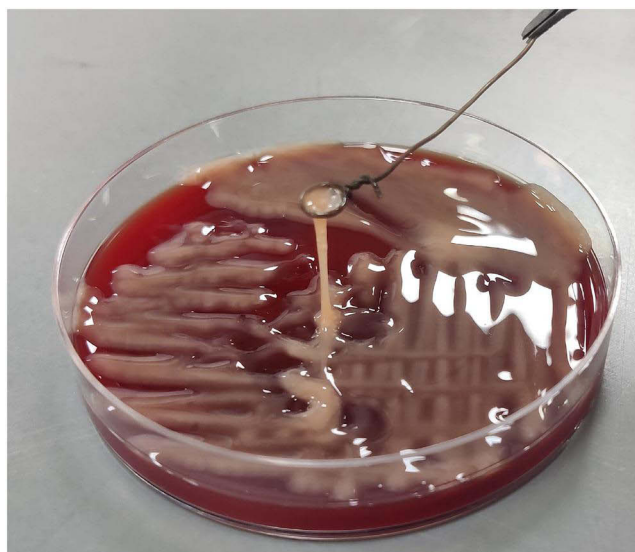


Figure 2 Representative image string test. Strings >5mm indicates the hypermucoviscous phenotype of the KP strain.

serotype of all the isolates was confirmed to be K64, which was validated by whole-genome sequencing. All isolates demonstrated hypermucoviscosity as shown by string length >5 mm in the string test (Figure 2). Common carbapenem resistance genes and virulence genes were identified by PCR using primers reported in the literature.^{17–19} All isolates presented β -lactam resistance gene *bla_{KPC}* but were negative for other carbapenemases including OXA-48, IMP, NDM and VIM. The KP strain from all five isolates possessed virulence factor plasmids *rmpA*, *mrkD*, *entB* and *ybtS*, which are related to mucoid phenotype, type-3 fimbrial adhesin, enterobactin and yersiniabactin, respectively.^{20,21}

The bacterial genome sequencing data obtained from pericardial effusion culture was compared against the Comprehensive Antibiotic Resistance Database (CARD) and Virulence Factor Database (VFDB). A total of 27 putative resistance genes were identified (Table 2), associated with three main resistance mechanisms: 1. The antibiotic efflux pump systems, prominently genes belonging to the ATP-binding cassette (ABC) and the major facilitator superfamily (MFS), 2. antibiotic inactivation or reduced permeability to target, which is induced by β -lactamase gene amplification and porin disruption, such as *bla_{kpc-1}*, *bla_{TEM-1}* and *bla_{CTX-M-65}*²² and 3. alteration in the target sites of antibiotics by *rmtB* gene encoding the aminoglycoside-modifying 16S rRNA methylase²³ and *sul2* gene encoding altered forms of dihydropteroate synthase that are not inhibited by the sulfonamides.²⁴ Furthermore, 31 virulence-associated genes were predicted, which suggested the employment of several iron uptake mechanisms in the patient isolate, including production of aerobactin (*iuc*), enterobactin (*entB*, *entA*, *fepC*, etc.) and secretion of yersiniabactin (*ybtS*, *ybtE*, *irp1*, *irp2*, etc.)^{25,26} (Table 3).

Based on the evidence of carbapenem resistance, the hypervirulence determinants, and the mucoid phenotype of the bacteria, we conclude that the infective agent identified in the isolates is sequence type 11 (ST11) capsular serotype K64 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-hvKP).

The serum survival of the CR-hvKP strain from the pericardial effusion, blood and ascites isolates was tested according to the previous description.²⁷ As shown in Figure 3, the colony-forming unit (CFU) recovery of all isolates was inhibited by the human serum time-dependently. After three hours of incubation, barely any CFU colony was visible in two samples and no colony growth was observed by the next day (Figure 3A and B), indicating a susceptibility of the KP strain to normal human serum.

Discussion

There are few reported cases of CR-hvKP infection related to purulent pericarditis. The patient reported here, with a history of type 2 diabetes mellitus and chronic renal failure, as well as recent thoracic surgery, died within a few hours

Table 2 Potential Resistance Genes from Pericardial Effusion Isolate, Predicted by CARD Annotation

Antibiotic Resistance Mechanism		Gene	Identity (%)	Result
Antibiotic efflux	ABC antibiotic efflux pump	msbA	80.62	+
		acrA	97.74	+
	RND antibiotic efflux pump	acrB	83.81	+
		mdtB	81.28	+
		mdtC	81.64	+
		baeR	81.63	+
		marA	81.57	+
		acrD	80.17	+
		mdtA	78.41	+
		mdtH	76.21	+
		mdtK	75.99	+
		tet(A)	100.00	+
	MFS antibiotic efflux pump	kpnG	99.49	+
		kpnE	99.45	+
		kpnH	84.16	+
		emrR	83.14	+
		mdfA	77.35	+
Antibiotic inactivation	CTX-M beta-lactamase	bla _{CTX-M-65}	100.00	+
	KPC beta-lactamase	bla _{kpc-I}	100.00	+
	Ambler class A beta-lactamase	LAP-2	100.00	+
	TEM beta-lactamase	bla _{TEM-I}	99.88	+
	Chloramphenicol acetyltransferase (CAT)	cat II	96.11	+
	Fosfomycin thiol transferase	fosA6	99.45	+
Antibiotic target replacement	Sulfonamide resistance	sul2	100.00	+
Reduced permeability to antibiotic	Porin with reduced permeability to beta-lactams	ompK37	95.24	+
Antibiotic target alteration	16S rRNA methyltransferase	rmtB	100	+
	Phosphoethanolamine transferase	pmrF	77.26	+

Notes: +: Genes aligned with identity >75% were considered positive.

of acute purulent pericarditis onset. The strain detected in the multi-site infection was confirmed to be the sequence type 11 (ST11) capsular serotype K64 carbapenem-resistant hypervirulent *Klebsiella pneumoniae* (CR-hvKP).

Cardiac tamponade secondary to massive pericardial effusion is the most severe complication of bacterial pericarditis. Without efficient treatment, the patient develops toxic shock, dyspnea and a sharp drop in heart rate, and death.² Great clinical acumen necessitates prompt diagnosis followed by emergent aggressive interventions of intravenous antibiotics to constrict infection deterioration or dissemination and adequate drainage to relieve the patient's cardiac compression.^{5,25,28,29} Both empirical use of broad-spectrum antibiotics and pathogen-specific antibiotic regimen should be considered.

The extensive use of antibiotics has rendered purulent pericarditis rare but also enabled the survival and multiplying of multi-drug resistant (MDR) bacteria. Another example of selective pressure favouring the survival of antibiotic-resistant bacteria is the irrational use of antibiotics in both clinical and agricultural settings.³⁰ The elderly population and individuals with inferior fitness or underlying health conditions such as diabetes mellitus, immunosuppression, chronic renal failure and previous surgical trauma are under the greatest threat.⁵ The shifting landscape of KP infection has drawn concerns over the emergence of KP “superbugs” armed with hypervirulence (hv) phenotypes, comprehensive resistance against common antibiotics, and the high transmissibility of the aggressive genetic elements.^{8,31–33} As carbapenem is currently reserved as physicians' last weapon against difficult-to-treat infections, the lurking danger of CR-hvKP could lead the infection from morbid to lethal. In a retrospective study performed in 2016, more than half (57%) of the hvKP infections were carbapenemase-producing.³⁴

Table 3 Potential Virulence-Associated Genes from Pericardial Effusion Isolate, Predicted by VFDB Annotation

Virulence Mechanism		Gene	Identity (%)	Result
Iron uptake system	Yersiniabactin	ybtU	100.00	+
		ybtQ	99.94	+
		ybtE	99.94	+
		ybtX	99.92	+
		ybtA	99.90	+
		fyuA	99.90	+
		ybtS	99.85	+
		ybtP	99.83	+
		irpI	99.88	+
		irp2	99.79	+
		ybtT	99.25	+
	Aerobactin	iucB	93.14	+
		iucC	90.63	+
		iutA	89.32	+
		iucA	88.75	+
		iucD	77.38	+
	Enterobactin	entB	82.31	+
		fepC	80.83	+
		entA	80.40	+
		fepG	79.61	+
		fepA	77.94	+
		entS	77.90	+
		fepB	77.11	+
		entE	76.94	+
		fepD	75.59	+
		fimE	75.70	+
Fimbriae	Type I fimbriae	fimA	75.14	+
Pilus structure	<i>Escherichia coli</i> common pilus structural subunit	yagZ/ecpA	89.90	+
	<i>Escherichia coli</i> common pilus chaperone	yagY/ecpB	86.40	+
		yagV/ecpE	84.39	+
	<i>Escherichia coli</i> common pilus usher	yagX/ecpC	87.61	+

Notes: +: Genes aligned with identity >75% were considered positive.

According to the recent literature, serotypes K1/K2 and MLST-11 are the most referred to as hypervirulent KP strains (hvKP) causing severe nosocomial infections.^{35,36} While K1 and K2 KP cause mostly liver abscesses or further disseminated infection³⁷ and ST11 (predominantly K64 serotype) imposes the highest hvKP prevalence in isolates

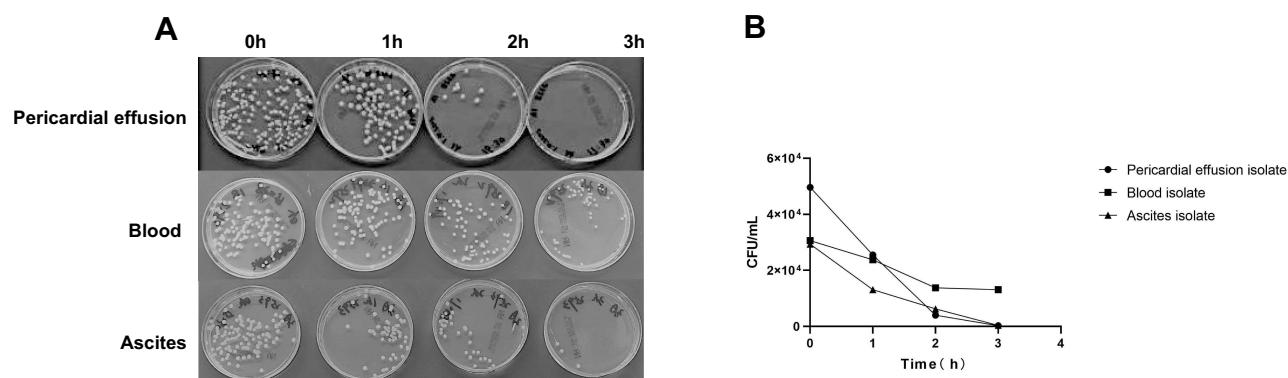


Figure 3 Serum survival assay of three isolates (pericardial, blood and ascites). **(A)** Colony-forming units (CFUs) recovery after co-incubation of the isolates with pooled normal serum on blood plates for 1, 2 and 3 hours. Images are representative of two parallel samples of each isolate. **(B)** Mean viable CFU counts of the replicates at each time point.

from various sources including blood sputum, urine, stool, wound and drainage.³⁸ ST11 CR-hvKP and its descendent sequence types such as ST258 have become the dominant clonal lineage in Asia, responsible for the recent outbreaks in some Chinese hospitals.^{12,18,39}

The ST11 hvKP strain detected in all five isolates of the patient in the present report carries the plasmid-borne *rmpA* gene accounting for the overproduction of extracapsular polysaccharide, which has been considered an independent factor conferring the hypermucoviscosity phenotype, thereby predisposing abscess formation.⁴⁰ Notably, the use of the terms hypermucoviscous KP (hmKP) and hvKP interchangeably to distinguish them from classic KP (cKP) is debatable. Compared to cKP, hmKP/hvKP is considered to insult mostly otherwise healthy populations and display hypermucoid appearance on agar plates.¹⁰ However, in vitro/in vivo and clinical studies have found that the morphological phenotype is not necessarily associated with high virulence. On the spectrum of many critical virulent factors that might constitute the minimum requirement for hypervirulence of hvKP, aerobactin is the most sensitive defining trait of hvKP.^{41,42} Genes encoding aerobactin (*iuc*) belong to the siderophore system, which mediates the elevated iron acquisition demanded by the survival of hvKP in host.⁴³ Indeed, the strain from the pericardial effuse isolate of the patient reported here has a positive VFDB- annotated *iuc* identity. Although the bacteria did not display resistance to healthy human serum, the patient's immune defence failed to fight against the dissemination because of her multimorbidity of diabetes mellitus, chronic kidney disease and complex surgery history.

The CR-hvKP strain was firstly detected from the blood and urine samples of the patient one month before the fatal incidence, which displayed the same virulence and carbapenem resistance genes. Although a full comparison of genetic mapping was not applied, we suspect that the occult bacteria at pulmonary focus multiplied and spread contiguously to pericardial space and other sites haematogenously, while the infection symptoms were controlled upon her discharge from the hospital. A lesson we have learned from this tragic case is that, in cases of CR-hvKP infections, vigilance may need to be extended to a follow-up tracing of the bacterial survival even after the patient appears symptom-free.

Conclusion

The *Klebsiella pneumoniae* strain identified in the fatal case of purulent pericardial was ST11-K64 CR-hvKP, consistent with the findings that ST11 dominates the carbapenem-resistant KP infections in China. Sporadic infection cases by similar strains have been identified in our hospital and seem to be increasing. As the advent and dissemination of the multidrug-resistant and highly virulent KP raises an alert, against the backdrop of population ageing and the rising prevalence of chronic conditions such as diabetes,⁴⁴ surveillance at epidemiological and molecular levels is paramount to avoid an endemic outbreak.

Abbreviations

KP, *Klebsiella pneumoniae*; PP, purulent pericarditis; MLST, multilocus sequence typing; ST, sequence type; cKP, classic *Klebsiella pneumoniae*; CRKP, carbapenem-resistant *Klebsiella pneumoniae*; hvKP, hypervirulent *Klebsiella pneumoniae*; EICU, emergency intensive care unit; PCR, polymerase chain reaction; CARD, comprehensive antibiotic resistance database; VFDB, virulence factor database; CR-hvKP, carbapenem-resistant hypervirulent *Klebsiella pneumoniae*.

Ethnic and Patient Consent

This case report was approved by the Ethics Committee of The Affiliated Hospital of Guizhou Medical University. Since the patient is deceased, written informed consent for publication of her clinical details and clinical images was obtained from the next of kin.

Author Contributions

SL and HC have contributed equally to this work and they are co-first authors. SL, HC and CZ acquired clinical data and performed the laboratory analyses. SL wrote the manuscript. HC reviewed the patient notes and revised the manuscript. YF and HC conceived the study, carried out the literature search, and processed the patient record. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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