


A Rare Case of Infective Endocarditis with Recurrent Fever Caused by *Elizabethkingia anophelis*

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Background: *Elizabethkingia anophelis*, an opportunistic pathogen that can cause infections in multiple parts of the human body, has multiple drug resistance and a high mortality rate. However, there have been few reports of infective endocarditis (IE) caused by *Elizabethkingia anophelis*, which means that diagnosis and treatment face challenges that cannot be ignored. Rapid and accurate identification and drug sensitivity results are needed to make timely treatment adjustments.

Case Presentation: An 81-year-old man presented with recurrent fever and increased infection index for more than a month. Based on his clinical symptoms, infection index, reduplicative blood cultures, and results of transesophageal echocardiography, he was ultimately diagnosed with infective endocarditis caused by *Elizabethkingia anophelis*. The patient had a favorable outcome with a 6-week course of intravenous antibiotic therapy.

Conclusion: This is a rare and successfully cured case of IE caused by the pathogen of *Elizabethkingia anophelis*, which is difficult not only in diagnosis but also in treatment. This case provides a certain referential significance to the treatment of *Elizabethkingia anophelis*-caused IE in clinical practice.

Keywords: *Elizabethkingia anophelis*, infective endocarditis, drug resistance, treatment

Introduction

Elizabethkingia anophelis, belonging to the genus *Elizabethkingia*, is a strain of Gram-negative, aerobic, oxidase-positive, oxidase-positive, indole-positive, non-fermenting, and non-motile bacillus.¹ It exists widely in natural environments such as soil and water and meanwhile can be also isolated from dry and moist clinical environmental and equipment surfaces and intravenous lipid solutions in the hospital.^{2,3} It is worth noting that *Elizabethkingia anophelis* is an emerging pathogen and has increasingly caused severe infections in human beings. The first case of neonatal meningitis infected by *Elizabethkingia anophelis* was reported in the Central Africa Republic in 2011.⁴ In recent years, there have been shocking outbreaks of *Elizabethkingia anophelis*-caused infections in Singapore, Hong Kong, Taiwan, the USA, and South Korea.^{5–10} It has been reported that the infection of *Elizabethkingia anophelis* had two prominent features: multiple drug resistance and high mortality,^{11,12} both of which seriously threaten human's life and health. The predisposition factors of *Elizabethkingia anophelis* infection include long-term use of antibiotics, immunosuppression, catheter retention, and prior invasive surgery. Moreover, *Elizabethkingia anophelis* can cause bacteraemia, eye infections, pneumonia, neonatal meningitis and so on.^{13–15} Unfortunately, people have limited understanding of *Elizabethkingia anophelis*, which poses an obstacle to the management of their infection. It is particularly noteworthy that *E. anophelis* has not been reported to cause IE, so there is a large gap in the management of *E. anophelis*-associated IE.

Here, we report the first case of IE caused by *Elizabethkingia anophelis*, with difficulties in the diagnosis and treatment because of concealed symptoms and drug resistance. In this case, IE was finally diagnosed through a variety of

examinations. *Elizabethkingia anophelis* developed induced resistance to multiple drugs in just one week, which brought great challenges to anti-infection therapy. Therefore, clinical attention should be paid to the early diagnosis of IE, new drug resistance phenotypes of bacteria and timely adjustments should be made.

Case Presentation

An 81-year-old male, with a history of hypertension and cerebral infarction, was admitted to hospital (The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China), due to recurrent fever for more than one month. On examination, he had a body temperature of 37.7°C, blood pressure of 118/60 mmHg, pulse rate of 97/min and respiratory rate of 28/min. Laboratory evaluation revealed increased white blood cell of $15.84 \times 10^9/L$, C-reactive protein 56.17mg/L and procalcitonin 2.77ng/mL. On the next day after admission, his both hands venous and central venous catheter (CVC) blood culture were reported positive after 16.1 hours. Blood culture smear showed gram-negative bacteria (G^{-b}) (Figure 1). After blood culture inoculation on Columbia blood agar, there were white, raised and moist colonies growing after 24h incubation (Figure 2). It was identified as *Elizabethkingia anophelis* by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) (bioMérieux, Marcy l'Etoile, France) (Figure 3). Bronchoalveolar lavage fluid (BALF) and next-generation sequencing (NGS) result revealed 17956 total reads corresponding to *Elizabethkingia anophelis*, with 30.7% coverage and 89% relative abundance in bacteria (Table 1). The antibiotic sensitivity profile of *Elizabethkingia anophelis* showed resistance to aztreonam and colistin (Table 2). Targeted antibiotic therapy with intravenous drip of meropenem 1.0 g every 8 h, vancomycin 0.5 g twice-daily (Q12H) and minocycline 100 mg once daily (QD) was started. His body temperature and inflammation indexes began to decrease on Day 4.

However, the patient began to experience recurrent fever from Day 7 onwards. *Elizabethkingia anophelis* strains were still repeatedly isolated from blood culture and sputum culture, and the results of metagenomic next-generation sequencing (mNGS) were consistent (Figure 4). The *Elizabethkingia anophelis* isolated on Day 8 developed resistance to β -lactam drugs (Table 2), so that the treatment was switched to omacycline 100 mg intravenously (i.v.) QD and polymyxin 750000 IU i.v. Q12H. Then, omacycline was first switched to tigecycline 75mg i.v. Q12H and then to cefoperazone-sulbactam 3 g iv. drip Q6H because of repeatedly positive blood cultures. In addition, levofloxacin 0.5g i.v. QD and trimethoprim-sulfamethoxazole 0.96 g nasal feeding every 6 h were added according to the antibiotic sensitivity profile of *Elizabethkingia anophelis*.

After re-adjusting the medication regimen, the patient still experienced recurrent fever for over 3 weeks, and *Elizabethkingia anophelis* strains were still isolated from blood culture for multiple times. During the process of actively searching for the primary infection site, combining chest X ray which indicated pneumonia (Figure 5) and transthoracic cardiac color ultrasound which found a vegetation found on the aortic valve (Figure 6), the diagnosis was considered as infectious endocarditis (IE). Taking into account the tissue concentration of sensitive drugs, the final antibiotherapy was

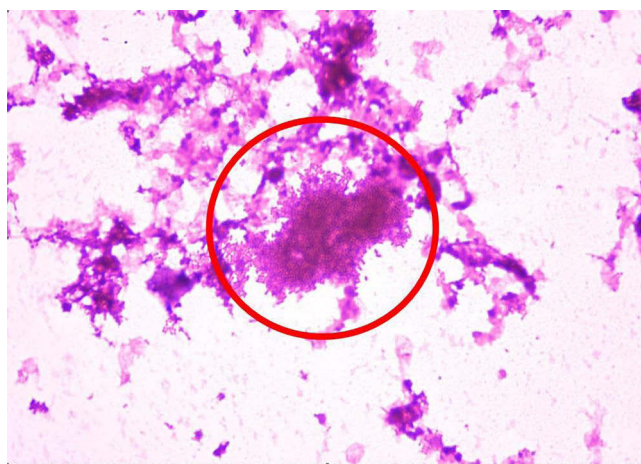


Figure 1 Blood culture smear showed gram-negative bacteria (as indicated by the red circle).



Figure 2 White, raised, moist colonies appeared on the blood-agar plate 24 h after incubation.

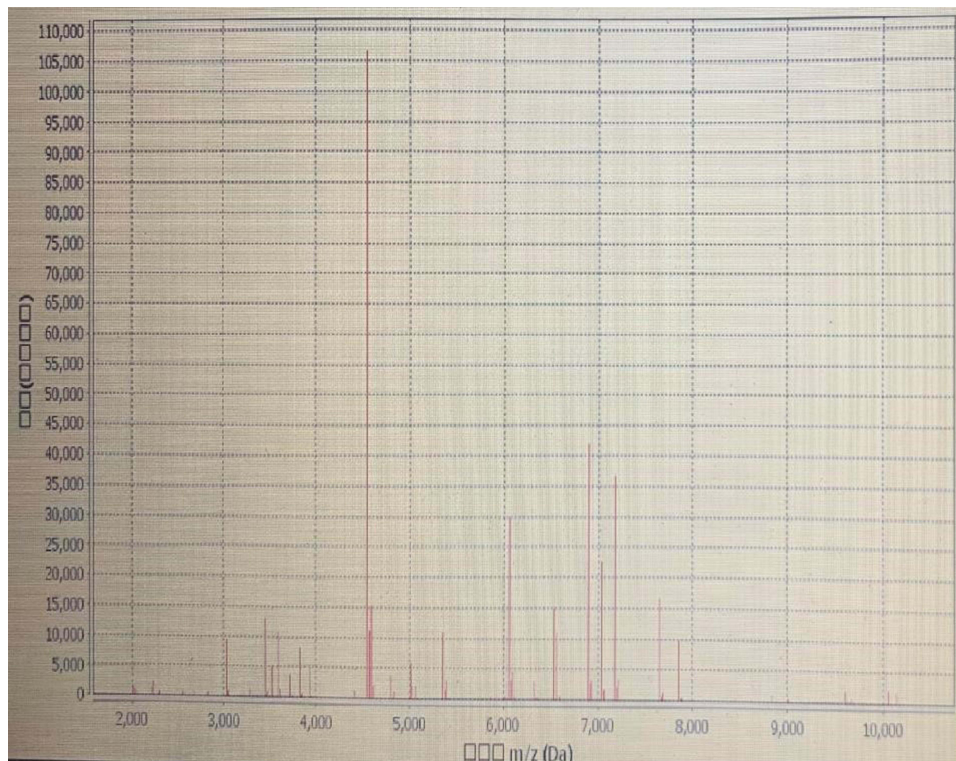


Figure 3 It was identified as *Elizabethkingia anophelis* by matrix-assisted laser desorption ionization time-of-flight mass spectrometry.

adjusted to cefoperazone sodium/ sulbactam sodium 3g i.v. every 6 hours (Q6H) and levofloxacin 0.75g i.v. QD. After one week of treatment, the patient's body temperature and inflammatory indicators gradually decreased to normal, and blood culture specimen also achieved microbial clearance. Due to the older age of the patient, surgical surgery was not recommended in clinical practice. The patient's condition improved and was discharged on Day 61.

Table 1 The Micro-Organisms Were Detected by BALF NGS on Day 3

Category	Pathogens	Reads	Coverage (%)	Relative abundance (%)	Confidence (%)
Bacteria	<i>Elizabethkingia anophelis</i>	17956	30.7	89.0	99
	<i>Chryseobacterium indologenes</i>	137	0.8	0.6	99
	<i>Staphylococcus aureus</i>	21	0.1	0.1	99
	<i>Enterobacter cloacae</i>	23	0.1	0.1	99
Fungi	–	–	–	–	–
Virus	–	–	–	–	–
Parasite	–	–	–	–	–
Specific pathogen	–	–	–	–	–
Human	<i>Candida parapsilosis</i>	10	0.1	40.4	99
Microeco-logical microflora	<i>Mycoplasma salivarium</i>	12	0.1	0.3	99

Table 2 The Antibiotic Sensitivity Profile of *Elizabethkingia Anophelis* from Blood Culture

Drug	Day 1		Day 8	
	Result	MIC ($\mu\text{g/mL}$)	Result	MIC ($\mu\text{g/mL}$)
Ticacillin/clavac acid	S	≤ 8	R	≥ 128
Piperacillin/Tazobactam	S	≤ 4	R	≥ 128
Cefepime	S	2	R	≥ 64
Cefoperazone/Sulbactam	S	≤ 8	I	32
Aztreonam	R	≥ 64	R	≥ 64
Meropenem	S	≤ 0.25	R	≥ 16
Imipenem	S	≤ 0.25	R	≥ 16
Tobramycin	S	≤ 1	R	≥ 16
Amikacin	S	≤ 2	R	≥ 64
Ciprofloxacin	S	≤ 0.25	S	1
Levofloxacin	S	≤ 0.12	S	0.5
Minocycline	S	≤ 1	S	≤ 1
Doxycycline	S	≤ 0.5	S	2
Tigecycline	S	≤ 0.5	S	2
Colistin	R	≥ 16	R	≥ 16
Trimethoprim-Sulfamethoxazole	S	≤ 20	S	40

Note: The interpretation criteria of drug susceptibility results were based on the MIC break point of other non-enterobacteriformes in CLSI 2023 M100.

Abbreviations: S, susceptible; R, resistant.

Discussion

Currently, people's knowledge about *Elizabethkingia anophelis* is still limited. It is worth noting that there have been several outbreaks of *Elizabethkingia anophelis*-associated infections worldwide in recent years. A hospital in South Korea reported that the infection rate of *Elizabethkingia anophelis* among inpatients increased from 0.02% in 2009 to 0.88% in 2017.⁸ The first outbreak of *Elizabethkingia anophelis* infection occurred in Singapore in 2012, resulting in 60% of deaths from sepsis.⁷ Moreover, *Elizabethkingia anophelis* infection occurred in Wisconsin, Illinois, and Michigan in the United States, which led to a mortality rate of 30.8%–70% during 2014 to 2016.^{5,6,9,10} It is proved that *Elizabethkingia anophelis* possesses a series of pathogenic factors, including capsule, lipopolysaccharide, endopeptidase, lipid biosynthesis and metabolites, magnesium transporters, heat shock protein, catalase, peroxidase, superoxide dismutase, etc.^{16,17} In particular, it is found that the species

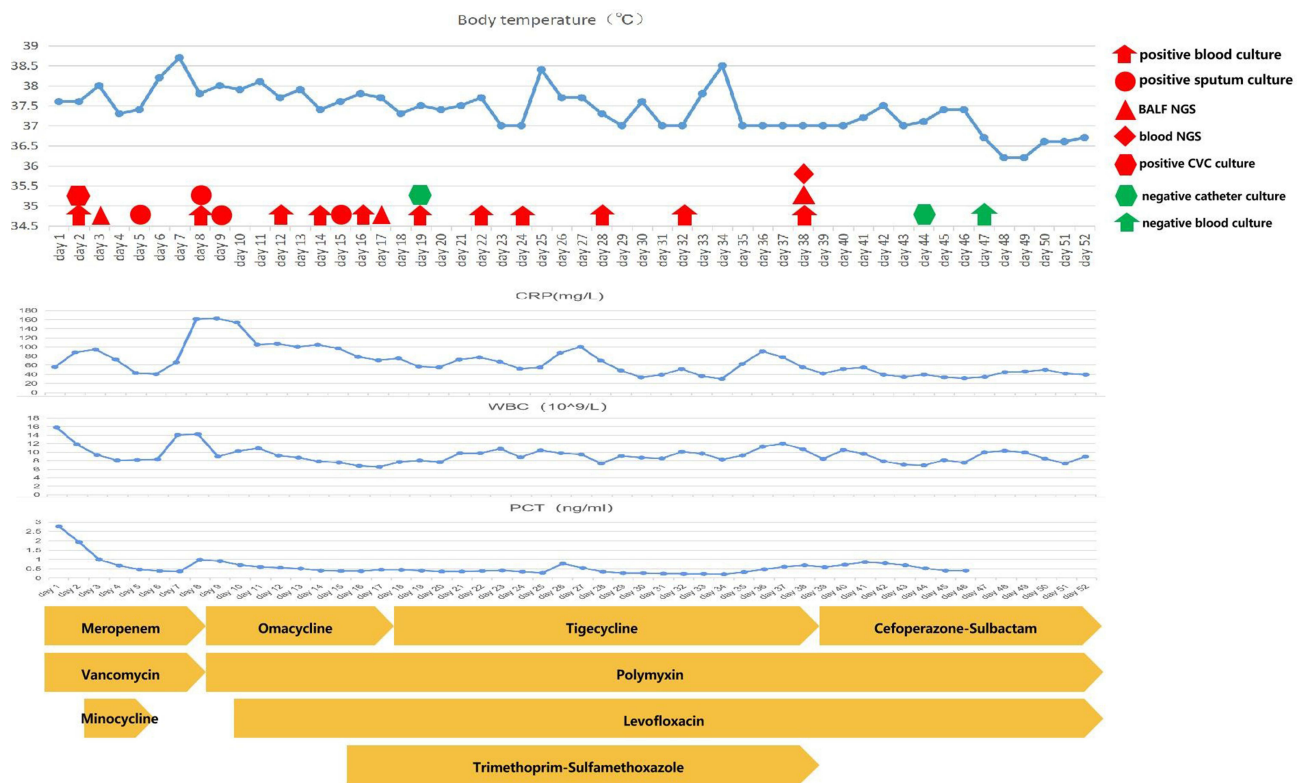


Figure 4 Treatment timeline including changes of Indicators of infection and etiology detection timepoints.



Figure 5 The chest X ray indicated pneumonia.

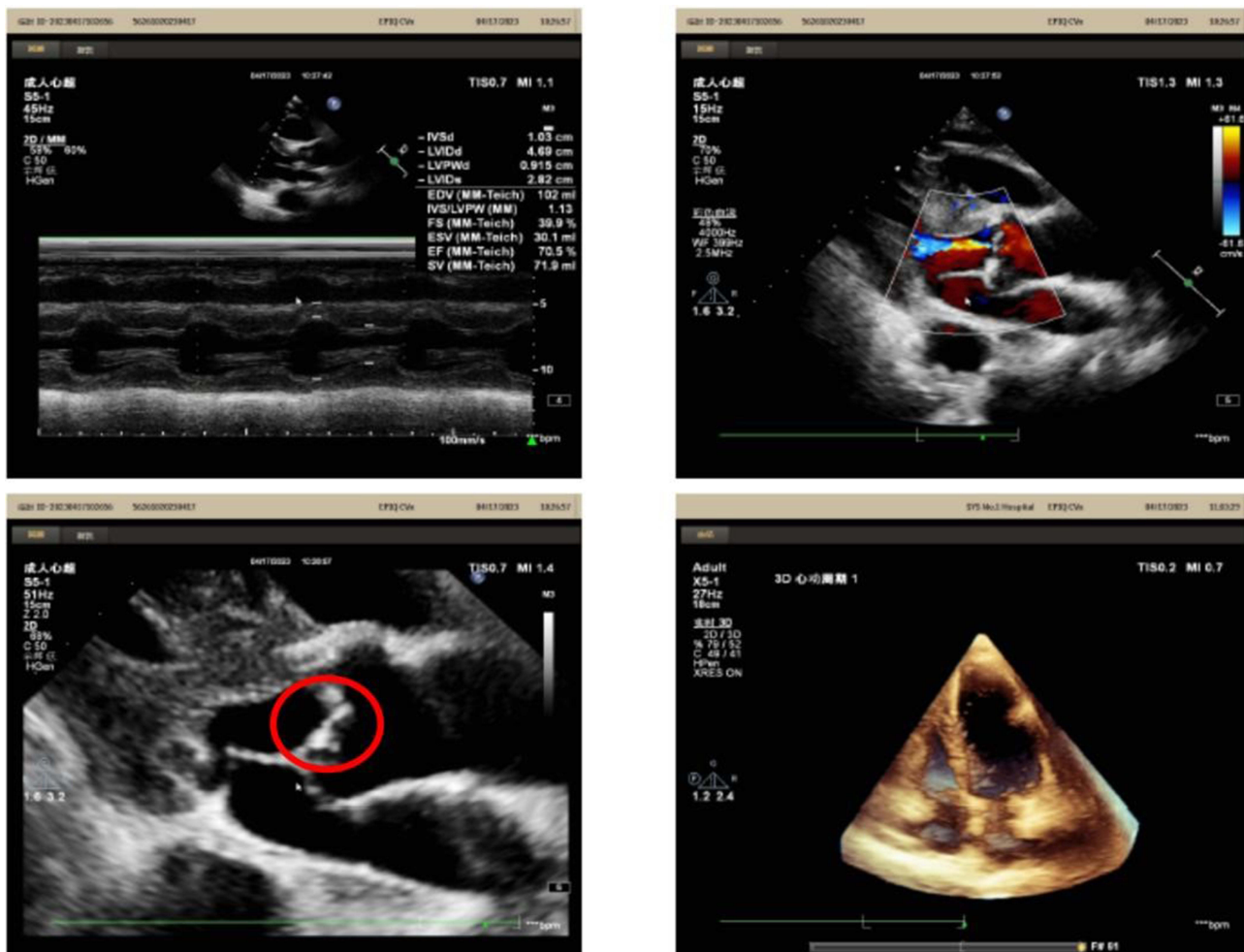


Figure 6 The echocardiograph images indicated existence of vegetation (as indicated by the red circle).

identification of *Elizabethkingia anophelis* is often misidentified as *E. meningoseptica* by VITEK 2 GN, API 20E and API 20NE systems,¹⁸ while it can be accurately identified by MALDI-TOF MS and 16S rRNA.³

Due to its ability to form biofilms, produce β -lactamases or encode efflux pumps genes, *Elizabethkingia anophelis* is resistant to many antibiotics commonly used clinical, such as β -lactam drugs and tetracycline.^{19–21} Whole-genome sequencing (WGS) revealed that *Elizabethkingia anophelis* carries serine beta-lactamase A (CME) gene and two metal- β -lactamases B (GOB and BLAB) genes on its chromosome. It is found that minocycline combined with levofloxacin is the most effective treatment against *Elizabethkingia anophelis*, when comparing to the regimen of minocycline or tigecycline combined with either ciprofloxacin in vitro and in vivo studies.²² YASMIN M et al²³ reported that the combination of ceftazidime-avibactam and aztreonam was ineffective against *Elizabethkingia anophelis* bacteremia and pneumonia in a patient with relapsed acute myelogenous leukemia, while cefiderocol contributed to the microbiologic clearance. In the present case, *Elizabethkingia anophelis* showed induced resistance to multiple drugs in just one week, which brought great challenges to treatment. Therefore, it is necessary to closely monitor the emergence of new drug-resistant phenotypes.

To our knowledge, this is the first case report on IE caused by *Elizabethkingia anophelis*. IE is a rare and life-threatening disease.²⁴ However, the diagnosis of IE usually requires a combination of clinical microbiological and echocardiography result. The pathogens commonly cause IE includes *Staphylococcus aureus*, *Streptococci viridans* and so on, but they have changed significantly due to the extensive use of broad-spectrum antibiotics, indicating that almost all known pathogenic microorganisms can cause IE.²⁵ According to the updated diagnostic criteria,²⁶ the patient's diagnosis meets one primary criterion (IE indicated by cardiac ultrasound) and three secondary criteria (host susceptibility factors, fever symptoms, and

pathogenic evidence). It was believed that in this patient, *Elizabethkingia anophelis* first caused respiratory infection, then spread into the blood to proliferate, reside and invade the originally normal aortic valve, eventually causing IE.

Conclusion

Elizabethkingia anophelis is a pathogen with high rate of drug resistance and increasing infection cases, which needs urgent attention. Further studies are required to enhance the awareness and develop effective therapies for *Elizabethkingia anophelis*-caused IE patients. Laboratories should improve the ability to identify the bacteria and monitor its drug resistance closely. Multidisciplinary communication is important so as to better reach the accurate diagnosis and treatment of infectious diseases.

Abbreviations

IE, infective endocarditis; CVC, central venous catheter; G^{-b}, gram-negative bacteria; MALDI-TOF MS, matrix-assisted laser desorption ionization-time-of-flight mass spectrometry; BALF, Bronchoalveolar lavage fluid; NGS, Next-generation sequencing; QD, Quaque die; mNGS, metagenomic next-generation sequencing; WGS, Whole-genome sequencing.

Ethics Approval and Consent to Participate

The study publication of the case details was approved by the Research Ethics Committee of The First Affiliated Hospital of Sun Yat-sen University approved the study ([2023]758). Consent for publication: Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; 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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