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CASE REPORT

Infective Endocarditis Caused by *Streptococcus Sinensis* in a Patient with Bioprosthetic Aortic Valve: A Case Report and Literature Review

Yannan Pan[1,2,*], Jiandan Qian[1,*], Guiqiang Wang[1], Hong Zhao[1]

[1]Department of Infectious Diseases, Peking University First Hospital, Beijing, People's Republic of China; [2]Department of Cardiology, Peking University First Hospital, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Guiqiang Wang; Hong Zhao, Department of Infectious Diseases, Peking University First Hospital, No. 8 Xishiku Street, Xicheng District, Beijing, 100034, People's Republic of China, Email john131212@126.com; zhaohong_pufh@bjmu.edu.cn

Background: Infective endocarditis caused by *Streptococcus sinensis* is exceedingly rare, with only limited cases reported. Here, we present the first documented case of prosthetic valve endocarditis attributed to *Streptococcus sinensis*.

Case Presentation: A 40-year-old Chinese female was admitted with a 45-day history of intermittent fever. The presumed diagnosis was a pulmonary infection and antibiotic therapies failed to alleviate her symptoms. On admission, infective endocarditis was suspected, considering the history of aortic valve replacement and recent dental procedure without prophylactic antibiotics. Transesophageal echocardiography disclosed a 3-millimeter vegetation in the prosthetic aortic valve, and metagenomic next-generation sequencing and mass spectrometry identified *Streptococcus sinensis*. The patient was diagnosed with infective endocarditis. Antibiotic treatments resulted in temporary clinical improvements, although fluctuations in temperature and inflammatory markers led to multiple attempts at antibiotic therapies. At last, the patient underwent an elective aortic valve replacement with a favorable prognosis.

Conclusion: In this case, we demonstrated prosthetic valve endocarditis caused by *Streptococcus sinensis*, which is an extremely rare pathogen. All reported endocarditis cases caused by *Streptococcus sinensis* were reviewed and summarized. Most of these patients had rheumatic heart diseases or congenital heart diseases. Antibiotic prophylaxis is important for high-risk procedures. Timely identification of the bacterium is crucial for diagnosis and treatment. Overall, infective endocarditis caused by this bacterium had a good prognosis.

Keywords: infective endocarditis, prosthetic valve, *Streptococcus sinensis*, metagenomic next-generation sequencing, case report

Introduction

Infective endocarditis (IE) is a rare disease that could be encountered during clinical practice, with viridans group Streptococci comprising 17% of causative organisms.[1] *Streptococcus sinensis*, a species of viridans streptococcus, was reported pathogenic for IE in 2002 for the first time.[2] Until now, few cases of *Streptococcus sinensis* IE have been reported in Asia and Europe, with the majority of patients having congenital heart diseases or chronic rheumatic heart diseases.[3,4] To our knowledge, all the reported cases were native valve endocarditis. Here, we reported the first case of prosthetic valve endocarditis caused by *Streptococcus sinensis* worldwide.

Case Presentation

A 40-year-old Chinese female came to our tertiary hospital with a chief complaint of intermittent fever for 45 days, with detailed timelines before admission shown in Figure 1. Initially, her body temperature ranged from 37 to 38.5 °C during daytime, and she received intravenous cephalosporin. Her temperature returned to normal but went up when she stopped the antibiotics. Chest computed tomography (CT) scans demonstrated inflammation in the right lower lobe. She was diagnosed with a pulmonary infection and received cephalosporins and azithromycin for 2 weeks. Ten days after discontinuing antibiotic therapies, her

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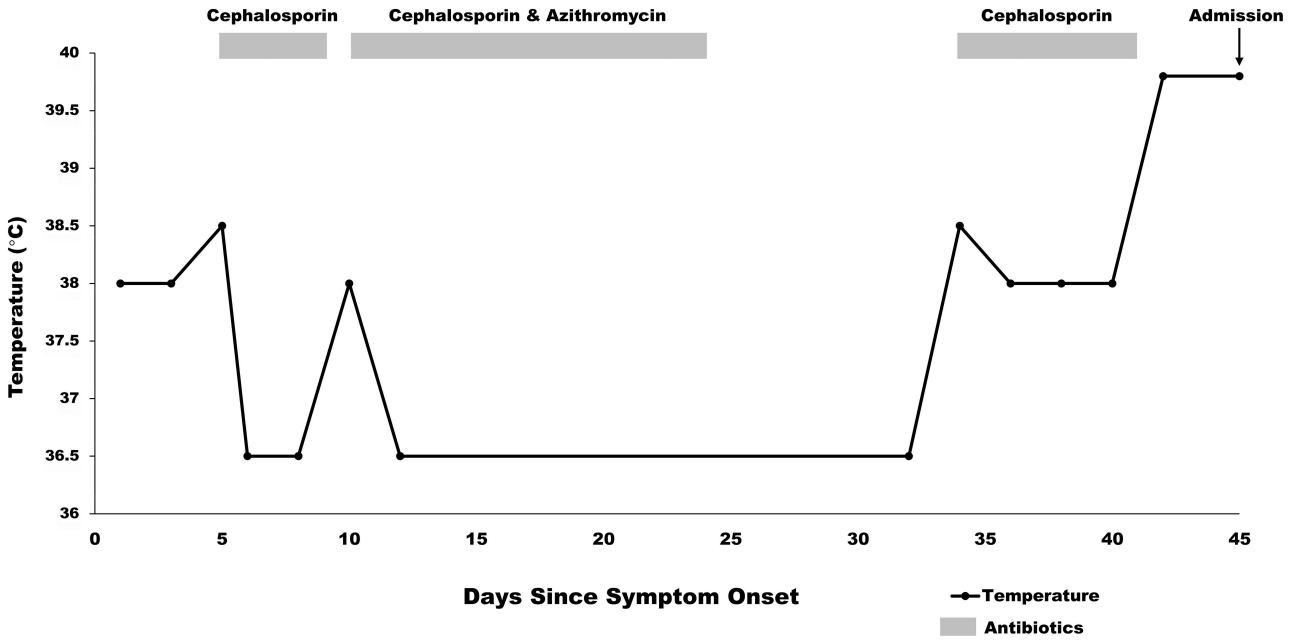

Figure 1 Timelines of body temperature and antibiotic therapies before admission.

temperature went up to 38.5 °C. Complete blood counts and repeated chest CT scans revealed no abnormalities. Two sets of blood cultures were both positive for Gram-positive bacteria without further identification. Transthoracic echocardiography (TTE) demonstrated increased transprosthetic valvular peak velocity. She was treated with oral cephalosporin. Four days before admission, she stopped antibiotics and had a high-grade fever of 39.8 °C. Meanwhile, an 8-millimeter erythematous tender lesion appeared on the left ring finger and automatically resolved 3 days later. The patient had no signs or symptoms of weakness or numbness, abdominal pain, or hematuria. Past medical history included bioprosthetic aortic valve replacement due to bicuspid aortic valve 11 years ago, and previous echocardiography showed bioprosthetic valve dysfunction. She underwent a dental filling procedure without prophylactic antibiotics 1 week before the onset of her symptoms. Physical examination showed a temperature of 38.8 °C and a grade 4 holosystolic murmur over the third intercostal space at the left sternal border.

On admission, the patient had a leukocyte count of $6.80*10^9$/L with 80.6% neutrophils. Erythrocyte sedimentation rate (ESR) was 27 mm/h, high-sensitivity C-reactive protein (hsCRP) was 38.37 mg/L, and procalcitonin was 0.18 ng/mL. Electrocardiogram and creatine kinase-MB were normal, while high-sensitivity troponin I (hsTnI) was elevated to 13.1 ng/L. Blood metagenomic next-generation sequencing (mNGS) and 2 sets of blood cultures were drawn. High-throughput sequencing was performed using the NextSeq CN500 platform, and details of mNGS are illustrated in Supplementary Methods. Within 24 hours, mNGS reported *Streptococcus sinensis* with a sequence number of 19 and a relative abundance of 21.84%. Empiric antimicrobial therapy with vancomycin was used. However, the patient had red rashes after intravenous vancomycin, and antibiotics were switched to penicillin G of 12 million units per day in 6 divided doses. Five days later, both sets of blood cultures were positive for gram-positive cocci, and *Streptococcus sinensis* was identified by matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry (MALDI Biotyper Microflex LT, Bruker, Germany). Antibiotic sensitivity tests are shown in Table 1. The pathogen was susceptible to penicillin G, and antibiotic therapies were not adjusted. Transthoracic echocardiography showed significant prosthetic aortic valve stenosis with mild regurgitation. Transesophageal echocardiography (TEE) indicated a 3-millimeter vegetation attached to the prosthetic valve, as shown in Figure 2.

Meeting 2 major (microbiology and imaging) and 3 minor (predisposition, fever, and immunologic phenomenon) 2023 Duke-International Society for Cardiovascular Infectious Diseases (ISCVID) Criteria,[5] the diagnosis of IE was confirmed. Complications were further evaluated. No embolisms were found through brain magnetic resonance imaging (MRI) and abdominal CT scans. As for immunologic phenomena, the patient had susceptible Osler's node before admission. Urinalysis and rheumatic factor test yielded negative results.

Table 1 Antibiotic Sensitivity Tests of Streptococcus Sinensis from Blood Culture

Antibiotics	Test Methods	Quantitive Results	Test Results
Vancomycin	KB test	24	Sensitive
Linezolid	KB test	24	Sensitive
Erythromycin	KB test	6	Resistant
Clindamycin	KB test	6	Resistant
Levofloxacin	KB test	28	Sensitive
Cefepime	KB test	38	Sensitive
Ceftriaxone	KB test	36	Sensitive
Cefotaxime	KB test	34	Sensitive
Penicillin G	Etest	0.024	Sensitive

Abbreviation: KB, Kirby-Bauer.

After confirming the diagnosis, an immediate cardiothoracic consultation was acquired. The patient was suggested to undergo surgical valve replacement as soon as possible. However, due to the small size of the vegetation, the patient declined immediate surgery and preferred a "wait-and-see" strategy with antibiotics.

After antibiotic therapies, the patient's temperature went back to normal (Figure 3). The patient had negative blood cultures after 2 weeks of penicillin G and switched to ceftriaxone 2 g per day for convenience to reduce the number of intravenous infusions. During the third week of hospitalization, the patient had a low-grade fever of 37.5 °C, and multiple tender red papules appeared on the finger, forearm and lower extremity (Figure 4). All the lesions resolved within 3 days, and they were regarded as Osler's nodes due to tender features despite uncommon locations. Antibiotics were switched to ceftriaxone 2 g per day and amikacin 0.6 g per day for another 2 weeks. After 6 weeks of antibiotic therapies, repeated TEE showed the vegetation was smaller in a narrow base with a length of 5 mm (Figure 2). Due to fluctuations in body temperature and inflammatory markers (Figure 3), antibiotics were switched to teicoplanin 800 mg per day and levofloxacin 750 mg per day for 2 weeks, and meropenem 1 g q6h for another 2 weeks. At last, the patient finally agreed to undergo surgical interventions and underwent an elective mechanical aortic valve replacement 10 weeks after

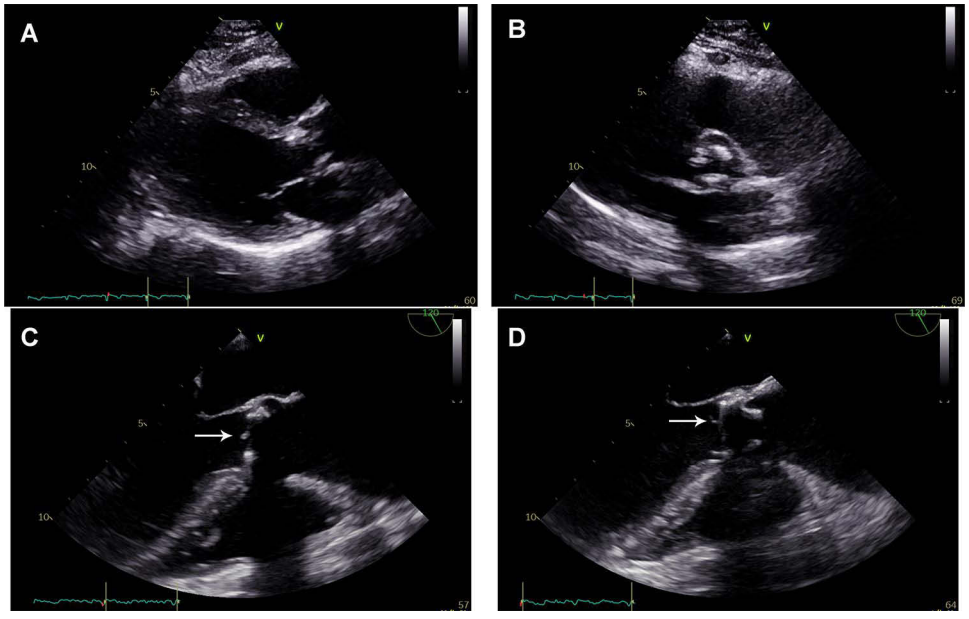

Figure 2 Transthoracic and transesophageal echocardiography of the patient.
Notes: Transthoracic parasternal long axis (**A**) and short axis (**B**) view of the prosthetic aortic valve. Transesophageal echocardiography on admission (**C**) and after 6 weeks (**D**) of antibiotic therapies, with white arrows pointed to the vegetation.

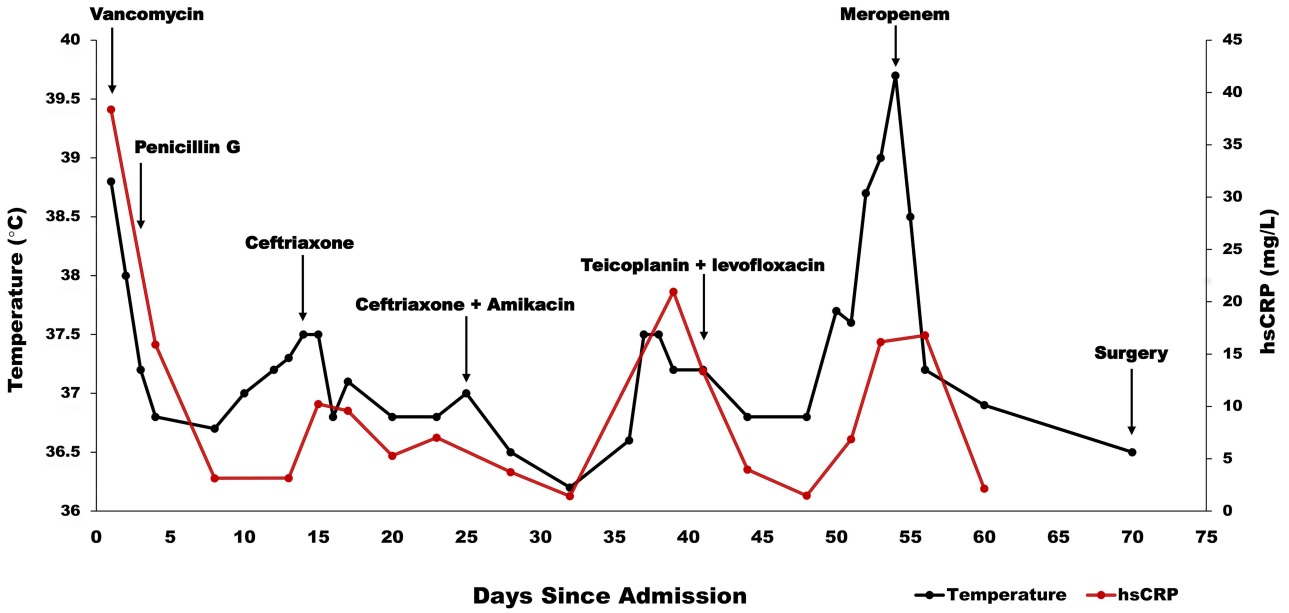

Figure 3 Timelines of daily body temperature, inflammatory markers, and antibiotic therapies after admission.

Figure 4 Tender red papules found during hospitalization.
Notes: Tender red papules on the finger (**A**), forearm (**B**), and lower extremity (**C**) are shown with black arrows.

diagnosis. Leaflet perforation was found during the surgical process, and mNGS of valvular tissue reported both *Streptococcus sinensis* and *Streptococcus sanguinis*. The surgery was successful, and no complications were reported during follow-ups.

Discussion

In this case, we presented a patient with refractory fever. Intermittent fever responding to antibiotic therapies made infectious diseases top of differential diagnoses, while the previous history of aortic valve replacement and recent dental procedure without prophylactic antibiotics led to the suspicious diagnosis of IE. The use of mNGS facilitated the identification of pathogenic bacteria *Streptococcus sinensis*, which had seldom been reported as the cause of IE. Timely empiric antibiotics were given, and TEE was performed, demonstrating aortic valve vegetation and confirming the diagnosis of IE. Results from blood cultures with mass spectrometry further confirmed the pathogen and provided antibiotic sensitivity tests that guided the choice of antibiotics. Prompt diagnosis resulted in a good prognosis for this patient. However, the reluctance to undergo early surgery postponed the whole treatment timeline.

Streptococcus sinensis was first reported in 2002 in Hong Kong, isolating from blood cultures of an IE patient and identifying molecular features by 16S ribosomal RNA (rRNA) gene sequencing.[2] This species belongs to viridans streptococci, speculated to be the ancestor of anginosus and mitis groups of streptococci.[6] Despite the name, the species has been reported in Hong Kong, mainland China, Thailand, Switzerland, France, the Netherlands, and Britain,[2,3,7–13]

Table 2 Literature Review of Reported Infective Endocarditis Cases Caused by Streptococcus Sinensis

Number	Reported Year	Age	Sex	Ethnicity	Preexisting Conditions	Previous Dental Manipulation	Diagnostic Methods	Strain	Infected Valves	Echocardiography Findings	Antibiotics & Duration	Surgical Intervention	Outcomes	References
1	2002	42	F	Asian	RHD	NA	BC (Agar Culture), 16S rRNA	HKU4^{T}	MV	No Vegetations	Ampicillin * 4 wks and Gentamicin * 2 wks	No	Survived	[2]
2	2004	NA	NA	Asian	RHD	NA	BC (Agar Culture), 16S rRNA	HKU5	NA	Vegetation	Penicillin G/Ampicillin, Gentamicin	NA	Survived	[4,6]
3	2004	NA	NA	Asian	RHD	NA	BC (Agar Culture), 16S rRNA	HKU6	NA	Vegetation	Penicillin G/Ampicillin, Gentamicin	NA	Survived	[4,6]
4	2007	57	M	Caucasian	RHD	Yes	BC (Agar Culture), 16S rRNA	Geneva	MV	Vegetation	Penicillin G * 3 wks and Gentamicin * 3wks, Ceftriaxone * 3 wks	Yes, Elective	Survived	[8]
5	2008	55	M	Caucasian	MVP	NA	BC (Agar Culture), 16S rRNA, *sod*A gene	HDP 2005–0155	MV	Cord Rupture	Amoxicillin * 4 wks and Gentamicin * 2 wks	Yes, Elective	Survived	[9]
6	2015	20	F	Asian	PDA	NA	BC (Mass Spectrometry), 16S rRNA	NA	AV	Vegetation	Amoxicillin & Gentamicin * 4 wks	Yes	Survived	[10]
7	2019	37	M	NA	NA	NA	BC (Mass Spectrometry), 16S rRNA, *sod*A gene	11026353	MV	Vegetation	Amoxicillin * 3 wks and Gentamicin * 1 wk	Yes	Survived	[11]
8	2019	63	M	Caucasian, Travel to Asia	NA	Yes	BC	NA	AV	Vegetation	Amoxicillin & Gentamicin, Penicillin G, Ceftriaxone	Yes	Survived	[12]
9	2020	58	M	Asian	No	NA	BC (Mass Spectrometry)	NA	AV, MV	Vegetation	Penicillin & Gentamicin	No	Death	[13]
10	2022	19	M	Asian	Bicuspid AV	NA	BC (Mass Spectrometry), 16S rRNA	BC1012612	AV, MV	Vegetation	Penicillin G & Gentamicin, Ceftriaxone, Teicoplanin & Meropenem	Yes	Survived	[3]
11	2024	40	F	Asian	Bioprosthetic AV	Yes	BC (Mass Spectrometry), mNGS	NA	AV	Vegetation	Penicillin G * 2 wks, Ceftriaxone * 4 wks and Amikacin * 2 wks, Teicoplanin & Levofloxacin * 2 wks, Meropenem * 2 wks	Yes, Elective	Survived	

Abbreviations: AV, aortic valve; BC, blood culture; F, female; M, male; MV, mitral valve; MVP, mitral valve prolapse; NA, not available; PDA, patent ductus arteriosus; RHD, rheumatic heart disease; wks, weeks.

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demonstrating its global prevalence. Cases have been reported in both Asians and Caucasians, with some having a travel history to Asia.[12] To our knowledge, the pathogen only infected endocardiums without documented infections elsewhere. Similar to other species of the viridans group, a previous study found a prevalence rate of 22% in saliva specimens from healthy volunteers,[14] indicating that the oral cavity served as the natural reservoir for *Streptococcus sinensis*. Indeed, at least 4 cases, including ours, reported previous dental manipulation before IE,[4,8,12] implying the importance of antibiotic prophylaxis in high-risk patients and procedures.[15]

A literature review of IE caused by *Streptococcus sinensis* is shown in Table 2. A total of 11 cases have been reported, with patient ages ranging from 19 to 63. Most patients had rheumatic heart diseases and congenital heart diseases, including mitral valve prolapse, patent ductus arteriosus, and bicuspid aortic valve. The majority of patients responded to β-lactams and aminoglycosides, and 63.6% underwent surgical interventions. One patient died due to severe comorbidities and refusal of surgery.[13] All the other patients had favorable outcomes.

For identification of the pathogen, unique phenotypic findings from Agar cultures and biochemical tests first revealed this novel species.[2] 16S rRNA gene sequencing further proved the species from a molecular level and demonstrated the phylogenetic relationship between *Streptococcus sinensis* and related species. The following cases confirmed the species by phylogenetic analysis of 16S rRNA and *sod*A gene.[9,11] In recent years, MALDI-TOF mass spectrometry has facilitated the rapid and cost-saving identification of pathogens with high sensitivity and specificity.[16,17] In our case, apart from mass spectrometry, we used mNGS for pathogen detection, greatly enhancing the diagnostic efficiency.

Specifically, this is the first case of prosthetic valve endocarditis caused by *Streptococcus sinensis*. For prophylaxis, antibiotics are recommended for prosthetic valve patients undergoing high-risk procedures, especially dental procedures.[18] For diagnosis, TTE might be suboptimal for prosthetic valves, and timely TEE is needed for clear visualization if clinical suspicion of IE is high.[18] At first, the patient chose a conservative treatment strategy, and antibiotic therapy duration was prolonged compared to those with native valve endocarditis who received 4 to 6 weeks of antibiotics. The latest guidelines have recommended oral antibiotic treatments in clinically stable patients.[18] However, this patient had fluctuations in temperature and inflammatory markers, indicating the need for long-term intravenous antibiotics. Surgery indications are different between native and prosthetic valve endocarditis. Surgery is considered the best treatment option for prosthetic valve endocarditis, while its exact timing is full of debate.[19] The patient had uncomplicated late prosthetic valve endocarditis caused by Streptococcus and declined early surgical intervention. However, close follow-ups showed fluctuations in temperature and inflammatory markers, which all pointed to the difficulty of conservative treatments with prosthetic valve endocarditis. Finally, the patient decided to undergo surgery, and an elective surgical replacement led to a good prognosis. Interestingly, mNGS of valvular tissue found both *Streptococcus sinensis* and *Streptococcus sanguinis*. It is possible that this patient had a coinfection of these bacteria, and antibiotic therapies might have led to changes in bacteria proportion.

Conclusion

In Conclusion, *Streptococcus sinensis* is pathogenic for IE, including prosthetic valve endocarditis. Most cases had Asian origins, but several reported European cases raised global concerns. Most patients had rheumatic heart diseases or congenital heart diseases. Antibiotic prophylaxis is important for high-risk procedures. Timely identification of the bacterium, including blood cultures with mass spectrometry and sensitivity tests, 16S rRNA gene sequencing, and mNGS, is crucial for subsequent diagnosis and treatment.

Abbreviations

IE, infective endocarditis; MALDI-TOF, matrix-assisted laser desorption ionization time-of-flight; mNGS, metagenomic next-generation sequencing; rRNA, ribosomal RNA; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Data Sharing Statement

The data generated or analyzed during this study are available from the corresponding authors, Dr. Hong Zhao or Dr. Guiqiang Wang, upon reasonable request.

Ethics Statement

Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the editor of this journal. This study was conducted with approval from the Ethics Committee of Peking University First Hospital.

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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 declare no competing interests.

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