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CASE REPORT

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Fatal case of streptococcal prosthetic valve endocarditis caused by *Streptococcus mitis* in patient with tetralogy fallot disorder: a case report

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Abstract

Background Prosthetic valve Endocarditis (PVE) is an uncommon but potentially life-threatening infection involves a valve prosthesis or annuloplasty ring. Streptococci, including *Streptococcus mitis* and enterococci are major etiological agents, with studies indicating their significant role in late-onset PVE in some regions of world, staphylococci have surpassed streptococci as the most frequent causative organism. Despite challenges in diagnosis, molecular methods offer high sensitivity.

Case presentation A 30-year-old female patient, Iranian, with a history of hypothyroidism, tetralogy of Fallot, and a bioprosthetic valve replacement and weakness after two months from exprience upper respiratory tract infection (URTI), was admitted with complaints of epistaxis, fever and worsening of shortness of breath. She exhibited symptoms of anemia, thrombocytopenia, elevated WBC, LDH, and D-dimer levels, along with splenomegaly, pleural effusions, and pulmonary congestion. Echocardiography revealed significant valve vegetation and RV failure. Despite comprehensive treatment, including cardiac surgery and antifungal therapy, her condition deteriorated, leading to cardiac arrest and death. Posthumous molecular analysis identified *S. mitis* as the causative agent, despite negative blood cultures.

Conclusions This case highlights the challenges of diagnosing and treating complex PVE, particularly when conventional cultures are negative. The detection of S. mitis through molecular methods underscores the importance of early and accurate identification of pathogens in guiding effective treatment.

Keywords Prosthetic valve endocarditis, *Streptococcus mitis*, Tetralogy of fallot, Case report, Iran

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Background

Prosthetic valve endocarditis (PVE) is an uncommon and potentially fatal complication involving replaced heart valves [1]. PVE accounts for 10–30% of all cases of infective endocarditis, which is more likely to occur in the first 3 months after valve surgery [2]. PVE may occur in 1–9% of patients [3]. Despite significant advances in the diagnosis and treatment of PVE, the mortality rate is significant and varies from 20 to 80% among affected patients [2]. According to reports, 36.5% of PVE cases are associated with nosocomial infections. It seems that the main causes of mortality in patients are persistent bacteremia, heart failure and, intracardiac abscess [4].

The main cause of PVE is staphylococci, and streptococci and enterococci are less involved in its occurrence. *Streptococcus viridans* are responsible for 10–13% of PVE cases [5, 6]. *Streptococcus* is an anaerobic and facultative Gram-positive bacterium of which more than 100 species have been identified so far. Although most of the identified species of this pathogen are known as normal flora and are often found in the skin, throat, and upper respiratory tract, they are known as one of the most aggressive bacteria [7]. Among the known species of this genus, 35 species are associated with the occurrence of infection in humans. *S. pneumoniae*, *S. pyogenes*, *S. agalactiae*, and *S. mutans* can be mentioned among the known species of infection in humans [8]. Among the species that cause endocarditis, of *streptococcus viridans*, which are the main flora of the mouth, are responsible for 76% of cases of streptococcal endocarditis, and *S. mitis* is the most common species [9].

The studies conducted in Iran on infective endocarditis caused by streptococci are very limited. During studies in Iran to identify potential pathogens that cause endocarditis in people using culture methods, *S. viridans* caused endocarditis in 11.8 and 6% of patients, respectively [10, 11]. The purpose of this study is case report of PVE caused by *S. mitis* infection, which was identified using molecular methods.

Case presentation

A 30 years old female patient, Iranian, with hypothyroidism, tetralogy fallot (history of two reconstructive surgeries at birth and 4 years old) and bioprosthetic valve replacement from 10 years ago admitted in Shariati hospital, on August 07, 2023. She had been complaining of weakness since two months ago, after experiencing upper respiratory tract infection (URTI).

During this period, she suffered from low-grade fever, exertional shortness of breath, and required multiple outpatient visits, as well as a one-day hospitalization at another facility. On the day of her emergency room visit, she reported a high-grade fever (38.8 °C), epistaxis, anorexia, and worsening shortness of breath.

She had been treated with Ferinject for anemia and received multiple doses of dexamethasone. A few days before her referral to Shariati Hospital, she was given antibiotics during a one-day hospitalization, though the medication's name was unknown. Additionally, the patient had arbitrarily discontinued her levothyroxine a month prior to her visit.

On physical examination, the patient's temperature was 36.4 °C (97.5 °F), blood pressure 102/50 mm Hg, heart rate 100 beats per minute, respiratory rate 23 breaths per minute, and oxygen saturation 84% while she was breathing ambient air. Decreased bilateral sound in the bases of both lungs in auscultation. Right ventricular impulse was prominent (RV heaves) and a harsh systolic ejection murmur in pulmonary valve position. The abdomen was soft, and non-tender. She had not any skin lesion and the conjunctiva was pale. According to the result of lab test, bicytopenia (anemia & thrombocytopenia) with a significant increase was observed in the amounts of WBC (21.45 10^{*3}/µl). Cardiac factors, including troponin I (0.1ng/dl) was normal, lactate dehydrogenase (LDH) (1050 U/L) and D-dimer (3.7 mg/dl) was increased, respectively (Table 1). A test for Human immunodefciency virus (HIV) RNA was negative. Three blood culture (B/C) samples were collected from the patient, each one hour apart, with 10 cc of blood per sample. All results were negative.

A urinalysis was normal.

Sonography of abdominopelvic showed that spleen was 147 mm (mild splenomegaly), liver parenchymal echo was increased (fatty liver grade 1), moderate free fluid in the pelvis and bilateral pleural effusions in the bases of both lungs. Chest CT scan showed left side mild to moderate plural effusion and a consolidation that is now progressing to cavitation and evidence of pulmonary congestion (Figs. 1 and 2).

Due to overt DIC (disseminated intravascular coagulation) with 8 score base on ISTH diagnostic scoring system for DIC caused by sepsis,, the patient received platelets, packed cells, cryoprecipitate and FFP (Fresh frozen plasma) in the emergency room, and then broad-spectrum antibiotic treatment with meropenem (2 gr stat and 1gr TDS) and vancomycin (20 mg/kg stat and 15 mg/kg BD) was started after the B/C were sent. PBS (Peripheral Blood Smear) was drawn due to bicytopenia, but the only significant finding was the presence of toxic granulation. According to his history of congenital heart disease as well as bicytopenia and splenomegaly, echocardiography was requested for her evaluation infective endocarditis (IE). In the transthoracic echocardiography (TTE), the evidence of small vegetations in the tricuspid valve, several large vegetations on the pulmonary valve (max 23*12 mm) with extensive degeneration of bioprostatic valve and severe dilatation of the right ventricle with a Left ventricle ejection fraction of (LV EF) 45%

Table 1 Laboratory finding of the patient

Test	Day 1(first visit)	Day 5 (clinical deterioration)	Day 7 (surgery day)	Day 8 (day of death)	Unit	Normal range
WBC	21.45*	11.64	19.4*	18.4*	10^{*3}/µl	4–9.8
HB	5.8¥	8.7¥	10¥	6.5¥	g/dl	12–15
PLT	18,000¥	36,000¥	117,000	146,000	10^{*3}/µl	140–440
Urea	24	20	29	45	mg/dl	15–40
Creatinine	1	0.8	0.9	2.2	mg/dl	0.6–1.3
Aspartate aminotransferase (AST)	29	30			U/L	< 31
Alanine Aminotransferase (ALT)	9	20			U/L	7–35
Alkaline phosphatase	248	189			U/L	44–147
Total Bilirubin	5.5*	2.7*			mg/dl	0.1–1.2
Lactate dehydrogenase (LDH)	1050*	733*			U/L	100–190
D-dimer	3.7*	10.5*			mg/L	0–0.05
Fibrinogen	54¥	150¥	152¥	237	mg/dl	200–400
FDP	5–20	> 20			mg/ml	< 5
C-reactive protein (CRP)	11*	5.5	8.4	21	mg/dl	< 6
PTT	120*	29	53*	> 120*	Seconds	25 to 35
INR	9*	1.2	2.06*	4.8*	-	2–3
Troponin I	0.1	0.3	0.2	0.1	ng/ml	Up to 0.3

*Increase, ¥ Decrease

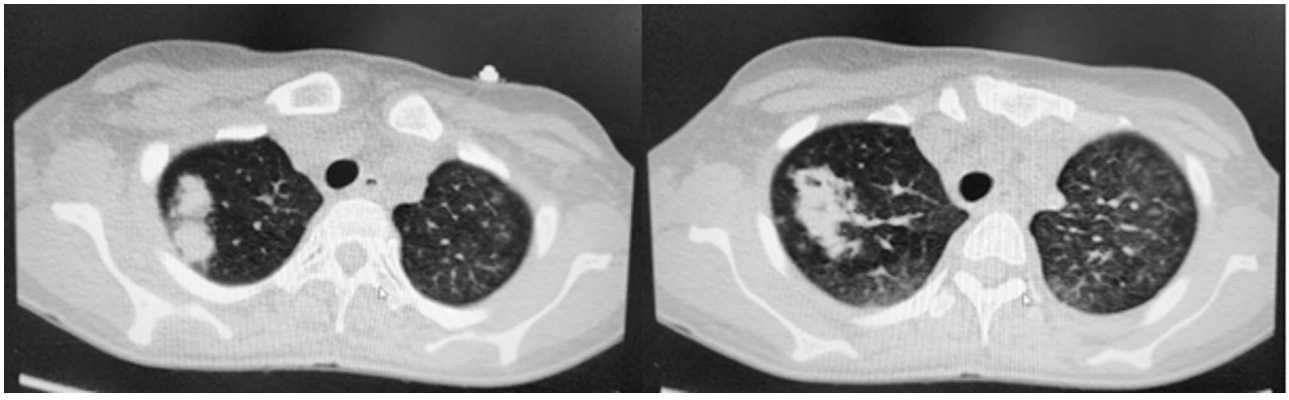

Fig. 1 Consolidation that is progressing to cavitation

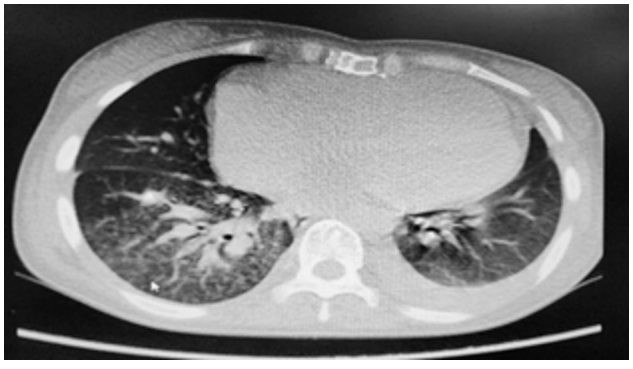

Fig. 2 Mild to moderate plural effusion and evidence of pulmonary congestion

were seen (Figs. 3, 4 and 5). With the diagnosis Prosthetic valve Endocarditis (PVE), and septic emboli, daily blood cultures were sent for bacterial and fungal, and antibiotic treatment with meropenem (2gr stat and 1gr TDS) and vancomycin (20 mg/kg stat and 15 mg/kg BD) was continued.

Due to shortness of breath and RV failure symptoms, treatment with diuretics was started. From day one cardiac surgery consultation was also adopted for the patient according to the size of the vegetation, overt DIC and pulmonary septic embolism and the patient was a candidate for emergency cardiac surgery after correction of coagulation disorders. Daily blood cultures were negative. *Brucella* PCR and serology tests wright and coomb's wright), were negative. Panfungal and panbactrial PCR of whole-blood specimens for assay the small-subunit rRNA gene sequence of the two major fungal organism groups and bacterial were negative too. Despite the negative

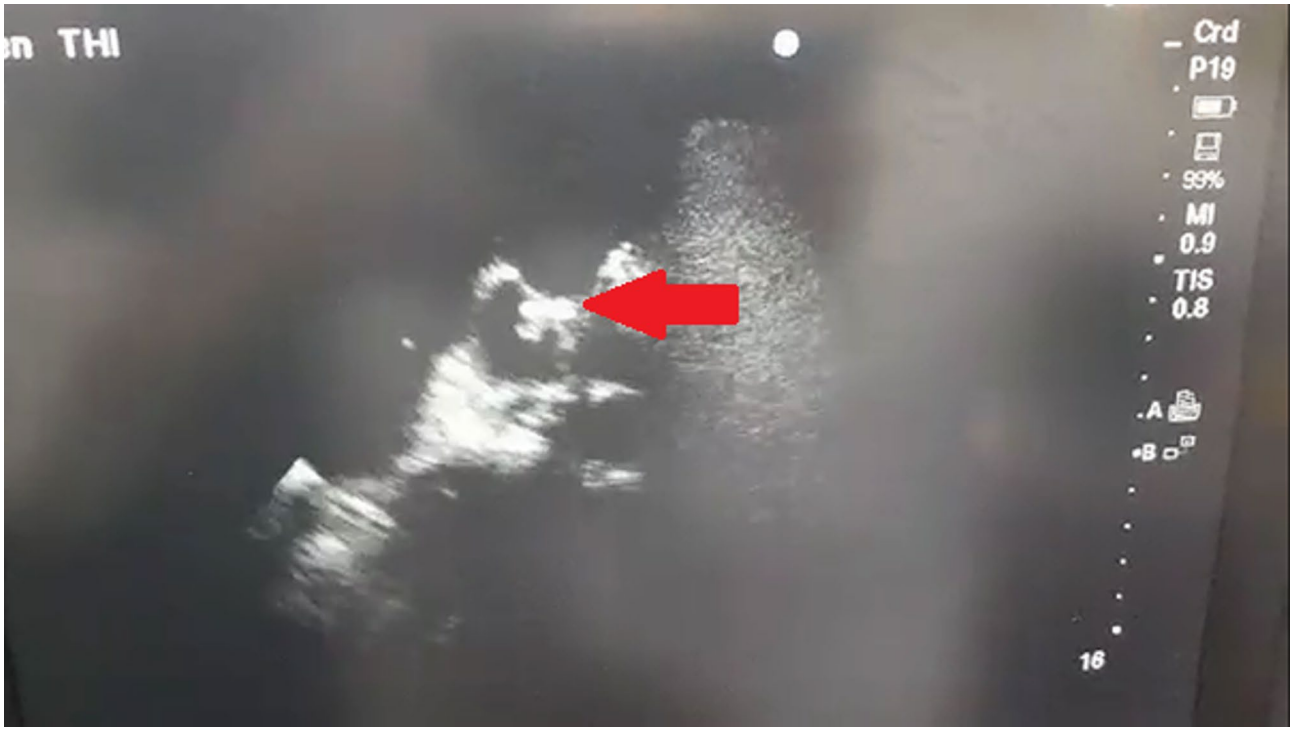

Fig. 3 Transthoracic echocardiography imaging. RV outflow view. Mobile echogenic pulmonary valve vegetation, with an oval shape, attached to the anterior leaflet (length 23 mm, thickness 10 mm)– Red arrow

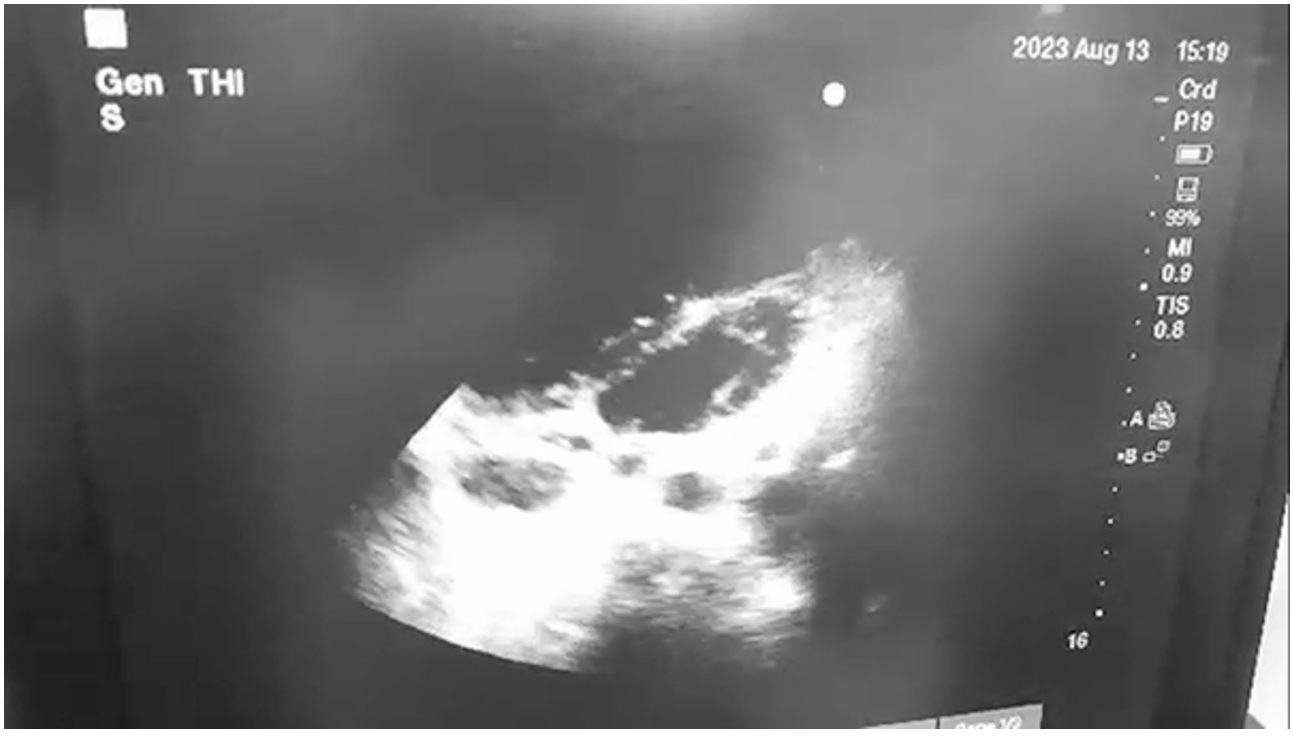

Fig. 4 Transthoracic echocardiography imaging. Short axis view at Mid ventricle level. D-shaped Left ventricle in and flattening of the interventricular septum suggests RV volume overload during diastole

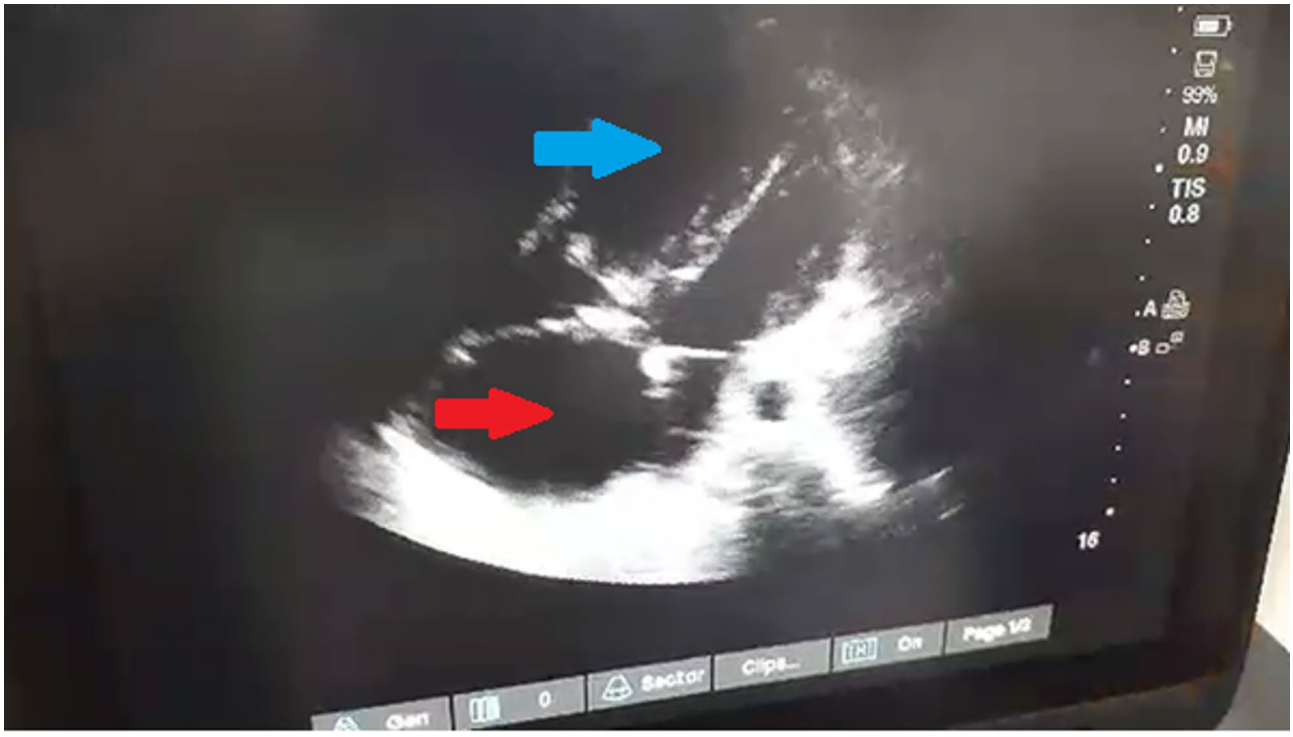

Fig. 5 Transthoracic echocardiography imaging. Four chamber off-axis view at. Severe RV (blue arrow) and RA dilation (red arrow)

fungal blood culture according to the size of the vegetation for the patient, Amphotericin B liposomal (5 mg/kg daily) was added to her medical treatment. During hospitalization, the patient's oxygen saturation suddenly dropped to 74% and shortness of breath exaggerated. Blood pressure was 100/31 mm Hg. Her temperature was 38.3 °C (100.9 °F), heart rate 140 beats per minute, respiratory rate 25 breaths per minute.

On the seventh day of hospitalization, while fully awake and alert but still experiencing severe shortness of breath, the patient underwent cardiac surgery (pulmonary valve replacement) after correction of coagulation abnormalities (platelet count and INR).

Under general anesthesia in the supine position, a redo sternotomy was performed following cannulation of the left and right femoral arteries. During the procedure, the patient developed ventricular tachycardia and was resuscitated with multiple shocks. After releasing extensive adhesions, the pulmonary artery was opened to remove the biodegenerated valve and a large vegetation. The degenerated valve was replaced with a bovine valve.

Additionally, the right atrium was opened, the tricuspid valve was repaired, and tissue samples from both the pulmonary (PV) and tricuspid valves (TV) were sent for smear and culture. The culture results were negative. Histopathological examination revealed fibro connective tissue containing fibrous material with acute inflammation.

The patient's blood sample and heart valves tissues were sent to Research Centre for Emerging and Re-emerging Infectious Diseases (RCERID) at the Pasteur Institute of Iran to investigate the causes of endocarditis with a negative culture. Unfortunately, one day later, while waiting for the test results sent to RCERID the patient's oxygen saturation decreased to 40% despite mechanical probably in the context of ARDS(Acute respiratory distress syndrome) and cosidering that the patient had OVERT DIC from the beginning of her hospitalization, despite surgery and infectious source control, she developed clinical symptoms such as active bleeding from the surgical site, the patient's drains and endotracheal tube and ultimately developed to decompensated DIC, which led to cardiorespiratory arrest and unfortunately the patient's expired, on August 15, 2023, 10 years after third surgery.

The result of blood sample and heart valves tissues sent to RCERID at the Pasteur Institute of Iran were reported as follows: serological and molecular test on both heart valve tissue and blood samples were reported as negative for *C. burnetii* and *Bartonella* spp., respectively. But surprisingly, despite the negative blood cultures, With additional phylogenetic studies including amplification and sequencing of 16 S rRNA Universal genes (27 F: 5′-AGAGTTTGATCMTGGCTCAG-3′, 1525R: 5′-AAGGAGGTGWTCCARCC-3′) [12], on pulmonary valve sample of patient, *S. mitis* infection was diagnosed based on sequencing results.

Discussion and conclusion

In this study, we reported a fatal case of Prosthetic valve Endocarditis (PVE) caused by *S. mitis* in Iran. *Streptococci* have different tendencies to cause infective endocarditis in people. Among the viridans group, *S. mitis*, which is known as the normal flora of the oral cavity, is one of the main causes of endocarditis in people with immunodeficiency or congenital heart diseases [13]. *S. mitis* is more likely to enter the bloodstream and cause serious infections than other viridans group streptococci (VGS). Moreover, unlike other members of this group, *S. mitis* rarely causes minor bacteremia, suggesting that it possesses intrinsic virulence properties that set it apart from other VGS [14].

Contamination of the prosthesis during surgery or in the early postoperative period, the use of blood products (plasma and cryoprecipitate), bloodstream infections (BSI) as a major risk factor, the need for open-chest re-surgery, invasive care, and long-term use of a central venous catheter, can all act as triggers for the occurrence of PVE [15]. It seems that the presence of heart valve tissue abnormalities and congenital heart diseases can be a risk factor for the occurrence of streptococcal endocarditis because it leads to the deposition of fibrins and the accumulation of platelets as a natural process for tissue repair, which conditions provide for the colonization of bacteria during transient bacteraemia [16, 17]. Our studied case also reported a history of valve replacement 10 years ago and tetralogy of fallot. *Streptococci* can induce platelet aggregation and adhesion to them and eventually lead to the occurrence of vegetation on the valve tissue [18]. The incidence of PVE is shown in the form of extensive vegetation and perforation, which is much larger than the vegetation of infectious endocarditis [1].

Few studies have investigated the incidence of PVE caused by *S. mitis*. In a study, a patient presented to the hospital with evidence of PVE, which confirmed bacteremia caused by *S. mitis* according to the blood culture results. Despite the antibiotic treatments, the patient did not respond to the treatment, and surgery was performed to replace the aortic valve and remove multiple abscesses. This is while *S. mitis* is not known as the cause of late PVE [19]. In our case, negative blood cultures and negative pan-bacterial PCR and tissue culture, delayed the diagnosis of streptococcal endocarditis with *S. mitis*. Of course, it should be noted that the valve culture results of patients with PVE remain negative in 11% of cases [2]. In a study, it was reported that a patient with PVE on a bioprosthetic aortic valve had a history of intravenous drug use. The patient's blood culture was reported positive for *S. mitis* on three consecutive occasions [20]. This is despite the fact that the blood culture was reported negative in the patient of our study, and vegetation was observed in the tricuspid valve and pulmonary valve.

In general, for diagnosis, blood culture methods and, in case of surgery, valve tissue culture is the first step to identify the infectious agent, but in our case, due to self-consumption of antibiotics and during a one-day stay in another hospital, result of blood cultures, were reported negative, so this prompted us to undergo molecular tests on the patient's tissue sample. Performing molecular tests on heart valve tissue samples has a very high sensitivity, so that the sensitivity of molecular methods is 90% compared to 31% for culture methods [18].

The best choice for the treatment of endocarditis caused by *S. mitis* is penicillin. Given the increasing resistance, alternative treatment strategies should be considered for cases that do not respond to penicillin. Vancomycin is the first-line alternative for penicillin-resistant *S. mitis*. The combination of vancomycin with an aminoglycoside (e.g., gentamicin) may produce synergistic effects, particularly in prosthetic valve endocarditis. Ceftriaxone, in combination with vancomycin, has also been considered to enhance efficacy in beta-lactam-resistant cases [20]. Despite the above results, our patient did not respond well to antibiotic treatment with meropenem and vancomycin and surgery, and unfortunately, because of the high risk of mortality in patients with streptococcal endocarditis, especially in cases of prosthetic valves and a history of congenital disease, she expired. The incidence of mortality in cases of streptococcal endocarditis is estimated between 15 and 50%, which requires careful examination of the cause of infective endocarditis [21]. Also, an important point that should not be overlooked in this patient is the initial referral with an overt DIC. Overt DIC is a rare but underdiagnosed event in emergency department patients. The degree of hypofibrinogenaemia on admission strongly and linearly predicted early death [22]. As mentioned in our case, fibrinogen was 54 (200–400 mg/dl), DIC score was 8 when we visited which was significant risk factor for early mortality, despite, appropriate treatment and surgery in our case.

Our case study is unusual complicated *S. mitis* PVE with negative blood and valve tissue culture which did not respond to empirical antibiotic treatment and reconstructive surgery, prompted us to inform clinicians of the necessity of early attention to molecular tests in similar complex cases to accurately diagnose the organism and determine the antibiogram to choose the appropriate antibiotic and once again emphasize the need for rational use of broad-spectrum antibiotics, especially in countries with limited resources.

Abbreviations

PVE	Prosthetic valve Endocarditis
VGS	Viridans group streptococcal
URTI	Upper Respiratory Tract Infection
LDH	Lactate Dehydrogenase
HIV	Human Immunodefciency Virus
(B/C)	Blood Culture

PBS	Peripheral Blood Smear
BSI	Bloodstream Infections
TV	Tricuspid Valves
PV	Pulmonary Valves
DIC	Disseminated Intravascular Coagulation
FFP	Fresh Frozen Plasma

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Author contributions
ZJ and ML integrated the data and wrote the manuscript, SE contributed the revision of the manuscript, SE and PA provided necessary assistance and provided key suggestions, SE, ZJ and ML contributed data acquisition and interpretation for etiological diagnosis. All authors reviewed and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
After receiving approval from the Research Ethics Committees of Shariati Hospital (IR.TUMS.SHARIATI.REC.1404.029), the case was reported.

Consent for publication
Unfortunately, the patient had passed away, so informed consent was obtained from a family member (his spouse) as his legal representative. All necessary explanations were provided to him.

Competing interests
The authors declare no competing interests.

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