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Early surgical intervention in culture-negative endocarditis of the aortic valve complicated by abscess in an infant: A case report

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Abstract

BACKGROUND

Surgical therapy of infective endocarditis (IE) involving aortic valves and mitral valves is widespread. However, there are few reports concerning patients with culture-negative endocarditis complicated by the appearance of comorbid valvular perforation and abscess. Therefore, real-time surveillance of changes in cardiac structure and function is critical for timely surgical management, especially in patients who do not respond to medical therapy.

CASE SUMMARY

Here, we report an atypical case in a 9-mo-old infant without congenital heart disease but with symptoms of intermittent fever and macular rashes. Physical examination, laboratory tests, and electrocardiograms suggested a diagnosis of IE, although the result of blood cultures was exactly negative. After treatment with antibiotic drugs, the patient got a transient recovery. On the 9th day, we proceeded with continuous echocardiogram due to fever again and the results revealed aortic valve abscess with perforation, regurgitation, vegetation, and pericardial effusion. Intraoperative monitoring revealed aortic valve perforation, presence of apothegmatic cystic spaces below the left coronary cusp of the aortic valve, and severe aortic valve regurgitation. Aortic valve repair was performed by autologous pericardial patch plasty. The patient was discharged after 4 wk of treatment and no complications occurred after surgery.

CONCLUSION

Our case demonstrated the necessity of serial echocardiography monitoring for possible adverse symptoms of IE in pediatric patients.

Key Words: Infective endocarditis; Aortic regurgitation; Abscess; Blood culture-negative;

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Core Tip: We report an atypical case in a 9-mo-old infant without congenital heart disease. Laboratory tests and electrocardiograms suggested a diagnosis of infective endocarditis (IE). After being treated with antibiotic drugs, the patient got a short recovery. Continuous echocardiographic examinations since admission revealed aortic valve abscess with perforation, regurgitation, vegetation, and effusion. Aortic valve repair was performed by using autologous pericardial patch plasty. No postoperative complications occurred and the patient was healthily discharged after 4 wk of treatment. Our case demonstrated the necessity of serial echocardiography monitoring in pediatric patients for possible adverse symptoms of IE.

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INTRODUCTION

Infective endocarditis (IE), although uncommon, is a vital disease with an annual incidence ranging between 0.05 and 0.12 cases per 1000 pediatric admissions[1]. The incidence of pediatric IE has significantly increased over the past two decades with changes in risk factors, causative agents, and clinical manifestations deeply impacting its epidemiology[2]. This could be attributed to the increasing use of invasive diagnostic and therapeutic procedures in the management of IE[3]. Further, advances in echocardiography and surgical techniques over the past few years have considerably enhanced the accuracy of diagnosis and treatment for IE, even in patients with a structurally normal heart[4].

IE in children with a normal heart has become a discernible clinical entity[1], which could plausibly be associated with a potential immunosuppressed condition[5]. In an estimated 8%-10% of pediatric cases, IE has been reported to be the consensus of one easily recognizable risk factor with a normally structured heart.

Culture-negative endocarditis is a clinically challenging entity both diagnostically and therapeutically. The spectrum of epidemiology of culture-negative endocarditis has changed over the last five decades. In a recently published series, approximately 8%-36% of patients with clinically diagnosed endocarditis had persistently negative blood cultures[6-8]. The most common causes of culture-negative endocarditis include previous receipt of antimicrobial therapy and infections caused by fastidious organisms also known as the "HACEK" group which includes nutritionally deficient *Streptococci*, *Pasturella spp.*, *Helicobacter spp.*, *Mycobacteria*, fungal organisms, infections involving intracellular organisms *Bartonella spp.*, *Tropheryma whippelii*, *Coxiella burnetii* (Q fever), and *Brucella spp.* that are either detectable by serology or polymerase chain reaction of valvular tissue[9]. Moreover, it has been shown that a lower sensitivity of blood cultures for yeast and complete lack of sensitivity for filamentous fungi make the diagnosis of fungal IE limited[1].

Although echocardiogram aids in clinically confirming the diagnosis of endocarditis, culture-negative endocarditis often delays diagnosis. And the higher morbidity associated with culture-negative endocarditis could be primarily attributed to the increasing burden of diagnostic testing, delays in administration of antibiotics, and the extensive use of broad-spectrum anti-microbial agents[10]. Culture-negative endocarditis complicated by the presence of valvular perforation and/or abscess calls for immediate surgical operation. Valvular perforation may lead to severe valve destruction, intractable heart failure, and even death if timely surgical therapy is not administered[11]. The presence of an abscess further increases surgical complexity due to excavation of the annular tissue during an ongoing infectious process, making it difficult to perform valve replacement or repair[12]. Recently, guidelines recommend

prolonging the duration of antibiotic treatment for the management of IE[1]. However, the indications for surgical intervention are not clearly explicit and are only limited to certain cases and indications[13]. In addition, most of the current indications are based on consensus[1].

Here, we describe a 9-mo-old infant who was diagnosed with culture-negative endocarditis and complicated with the appearance of valvular perforation and abscess, but did not suffer from congenital heart disease. Further, in view of the above and the scarcity of literature on early surgical therapy in culture-negative endocarditis, we assessed the factors leading to severe valve destruction, the recognition of which is critical and timely for surgical intervention, especially for patients who do not respond to medical therapy.

CASE PRESENTATION

Chief complaints

A male infant aged 9 mo and 8 d, weighing 8 kg, born *via* spontaneous vaginal delivery, was presented to the emergency department for evaluation of intermittent fevers and red macula.

History of present illness

The patient had intermittent fever (less than 39 °C), red macula, dry and chapped lips, and a red rash around the mouth for 9 d. No other symptoms such as nausea, vomiting, diarrhea, and urinary symptoms were present. He was admitted to the hospital with a presumptive clinical diagnosis of Kawasaki disease on May 12, 2019.

History of past illness

The patient's past medical history, family medical history, and vaccination status were insignificant.

Physical examination

On physical examination, the patient was conscious and comfortable and responded well. He was febrile with a temperature of 38.7 °C, had tachycardia with a heart rate of 142 beats per minute, but was hemodynamically stable with a normal respiratory rate of 34 breaths/min and normal blood pressure of 80/64 mmHg.

The sound of his breath in both lungs was rough and his neck was supple without lymphadenopathy. Skin examination showed red, needle-point-sized and maculopapular rashes that were non-itchy, faded under pressure, and were distributed on his trunk. Heart examination revealed slightly rough systolic murmur over the third and fourth intercostal space at the left sternal border. Abdominal examination was unremarkable.

Laboratory examinations

Laboratory tests revealed an increased white blood cell count at $32.4 \times 10^9/L$ (reference range: $10-13 \times 10^9/L$) and mild anemia with a hemoglobin level of 78 g/dL (reference range: 100-120 g/dL). The level of brain natriuretic peptide was mildly elevated. The levels of anti-streptolysin O, rheumatoid factors, C-reaction protein (CRP), and myocardial injury markers were normal; urine and stool tests for tetracycline hydrochloride, biochemical tests for antinuclear antibodies, and functional test for the thyroid were negative.

Imaging examinations

Chest computed tomography suggested the possibility of pneumonia following the admission. B-mode ultrasonography of the neck showed two to three enlarged cervical lymph nodes measuring $1.5 \text{ cm} \times 1.5 \text{ cm}$ with good mobility. No abnormalities were observed in the liver and spleen.

Five consecutive sets of electrocardiograms (ECGs) revealed ST segment depression and a flat T wave. On the 9th day, he developed a high-grade fever (38.4 °C), and color Doppler echocardiography revealed abscess with perforation in addition to the vegetation, aortic regurgitation, and pericardial effusion (Figure 1A). Color Doppler echocardiography was performed thrice on the 2nd (May 13), 6th (May 17), and 9th day (May 20) post-admission (Figure 1).

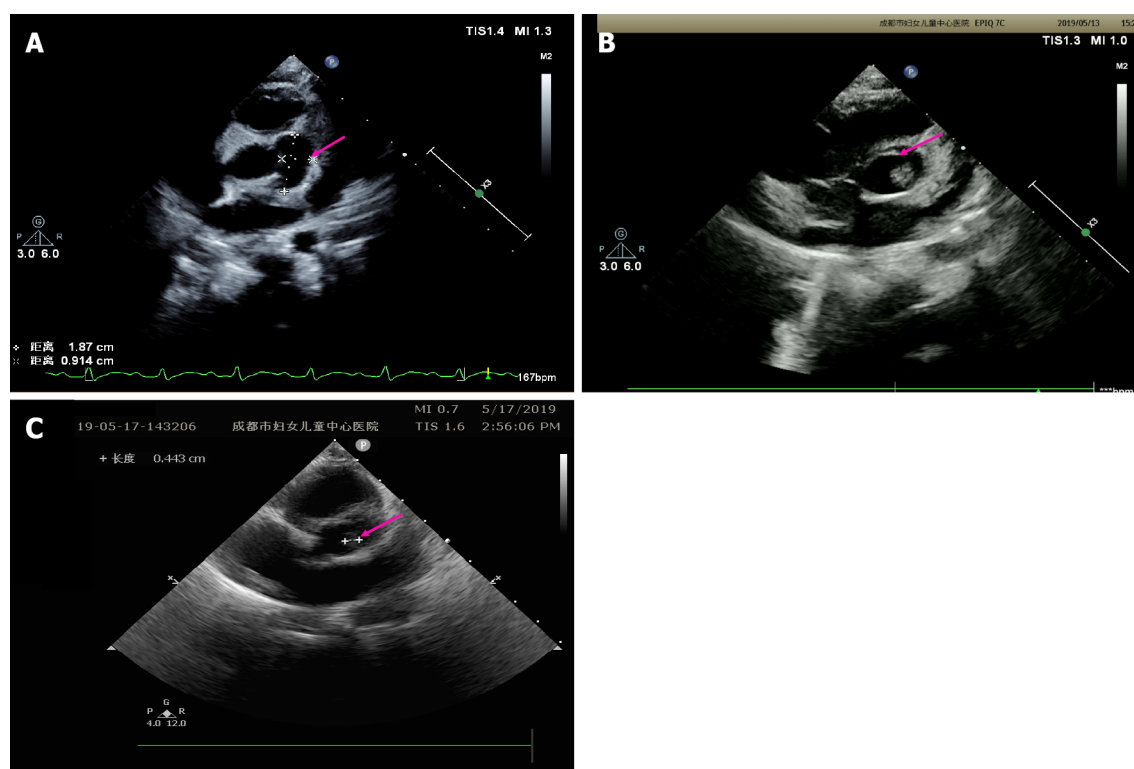


Figure 1 Preoperative color Doppler echocardiograms. A: Preoperative color Doppler echocardiogram, acquired on the 9th day (May 20, 2019), revealing abscess with perforation, minor aortic regurgitation, and minor to moderate pericardial effusion (arrow); B and C: Preoperative color Doppler echocardiograms, acquired on May 13, 2019, revealing that there was vegetation attaching on the left ventricular surface of the left coronary aortic valve (arrow). The measured value of left ventricular systolic function was normal.

Microbiological identification of potential causative agent

Four consecutive sets of blood cultures were performed and all of them were negative (May 12/13/17/20, 2019). Although positive blood cultures with Gram-positive cocci were reported from another hospital but paper reports were unavailable.

Further diagnostic work-up

After admission, the patient did not meet the diagnostic criteria for typical Kawasaki disease and incomplete Kawasaki disease after re-evaluation according to the American Heart Association guidelines in 2017, so infectious disease was considered. He started intravenous piperacillin sulbactam and cefazolin for 8 d. Following the initiation of antibiotics, his clinical symptoms improved significantly. His sensorium and body temperature were normal, respiratory status improved, and heart sound was louder and audible with an even heart rhythm besides rashes on his trunk and limbs disappeared.

However, on the 9th day, he developed a high-grade fever (38.4 °C). A definite diagnosis was attained considering the clinical features as well as the results of laboratory tests and UCGs.

FINAL DIAGNOSIS

The final diagnosis of the presented case was culture-negative endocarditis.

TREATMENT

On the 10th day, aortic valve repair was planned for assistance in management. During surgery, no significant enlargements of the heart and aorta/pulmonary artery (1:1) were seen; aortic valve perforation, severe aortic regurgitation, vegetation, and apothegmatic cystic spaces on the left coronary cusp of the aortic valve were identified. Multiple vegetations were surgically excised from the left coronary cusp of

the aortic valve. The abscess of the inferior aortic valve was drained. The left coronary valve was repaired by using autologous pericardial patch plasty, and the perforation of the left ventricle was closed with direct sutures.

OUTCOME AND FOLLOW-UP

The follow-up evaluations included complete medical history, clinical examination, and color Doppler echocardiography. Following surgery, the culture of vegetation obtained during surgery was negative. Two sets of blood cultures were documented to be negative. Postoperative reexamination of echocardiogram at weeks 2, 3, and 4 showed mild aortic regurgitation, normal cystic echo of the left coronary valve, and normal left ventricular systolic function (Figure 2). After 4 wk of treatment with intravenous piperacillin sulbactam (245 mg/kg/d, q8h), the patient was healthily discharged.

DISCUSSION

We describe the case of a 9-mo-old male infant who presented with intermittent fever and macular rashes that were persistent for 9 d after the admission. On our evaluation, the patient was febrile with a temperature of 38.7 °C, had tachycardia with a heart rate of 142 beats per minute, and had a slightly rough systolic murmur over the third and fourth intercostal space at the border of the left sternum. Persistent and “apparently” negative blood cultures together with ECGs and color Doppler echocardiogram confirmed the clinical diagnosis of culture-negative IE. According to the revised Duke criteria, the diagnosis and classification of IE mainly depend on blood culture.

However, the sensitivity of these criteria for diagnosing culture-negative endocarditis is ambiguous[14]. Of note, a previous study has observed a significantly higher prevalence of “possible endocarditis” in patients with negative cultures and further demonstrated that patients with culture-negative endocarditis were less likely to be classified as “definite endocarditis” by the revised Duke criteria[15]. Taken together, these studies suggest that the criteria for the diagnosis of pediatric culture-negative IE are variable and need to be carefully evaluated individually on a case-by-case basis.

It is thought that culture-negative endocarditis in patients with prior antibiotic therapy is caused by Gram-positive cocci, such as *Staphylococci*, *Streptococci*, and *Enterococci* – the bacteria usually associated with culture-positive endocarditis[16].

The possibility of “culture-negative” endocarditis after antibiotic use arises in our case as blood culture was carried out prior to the initiation of empirical antimicrobial therapy. Thereby, echocardiography is a crucial tool in the diagnosis and management of culture-negative endocarditis in the absence of positive blood cultures. In this case, we had performed serial color Doppler echocardiography for monitoring the minor changes of cardiac structure and coronary condition to ensure timely interventions before any possible clinical deterioration. We detected the vegetation and abscess in time, and then arranged surgery immediately under the condition that antibiotic treatments were not well responded to. Similarly, earlier studies have shown that in adult patients with culture-negative endocarditis and large vegetation, monitoring vegetation size by means of serial transesophageal echocardiography might prove to be useful to determine the efficacy of treatment[17].

Given that the patient had a structurally normal heart and did not show any risk factors for congenital heart disease, the clinical situation resembles atypical culture-negative IE. It is thought that many factors predispose pediatric patients with IE to potentially life-threatening complications that call for an early surgery[1]. Although a latent heart disease is the main predisposing factor for pediatric IE, many cases of IE without a preexisting heart disease have been reported[18]. A study by Zamorano *et al* [19] showed that patients with culture-negative IE have a higher rate of complications, such as valve rupture and perforation requiring immediate surgical attention, compared to those with positive blood culture. There is a paucity of data about pediatric IE with a normally structured heart and without predisposing factors. Of note, a review by Russell *et al*[20] related to the surgical outcome of IE identified that, of 35 cases of endocarditis requiring surgical intervention, 14 (40%) presented with no potential congenital heart defect. Other possible latent factors such as immunodeficiency, chronic parenteral nutrition, and those with central venous catheters near the heart or tunneled central venous catheters could be considered as predisposing conditions for IE[1]. A study by Carceller *et al*[21] showed that approximately 26% of

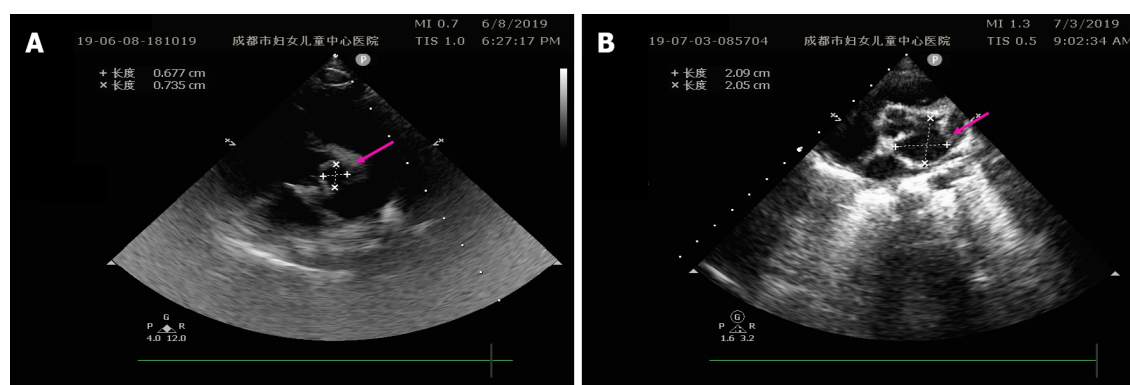


Figure 2 Postoperative color Doppler echocardiograms. A: Postoperative color Doppler echocardiogram, acquired on June 8, 2019, revealing mild aortic regurgitation (arrow). The lateral cystic echo of the aortic valve was narrower than that of the anterior aortic root, observed on May 20, 2019. The left ventricular systolic function was normal; B: Postoperative color Doppler echocardiogram, acquired on July 3, 2019, revealing mild aortic regurgitation (arrow). The lateral cystic echo of the aortic valve was enlarged compared with that of the previous echocardiogram (June 8, 2019). The left ventricular systolic function was normal.

pediatric patients with IE had a serious systemic underlying disease without congenital heart defect, and about 7% were completely healthy. However, these potential predisposing factors were not identified in this case.

Interestingly, the lesion was located on the left side in this case, similar to that reported by Pachirat *et al*[22] who showed that about 92% of patients had lesions located on the left side in contrast to only 8% on the right side.

Furthermore, Shamszad *et al*[23] demonstrated that the left-sided lesions were the most that needed surgical intervention. The complex nature of this disease necessitates surgical treatment in about one half of patients with IE[13]. According to the guidelines (2016) published by the American Association for Thoracic Surgery, surgical indications for IE include severely-compromised valve function resulting in symptoms of heart failure, left-sided IE caused by *Staphylococcus aureus*, fungi, or other highly resistant microorganisms, IE complicated by a heart block, annular or aortic abscess or penetrating lesions, and persistent infection for 5-7 d despite an appropriate antibiotic course[24]. Irrespective of whether the nature of IE is culture-positive or culture-negative, the major indications for surgical treatment to prevent embolization are the presence of left-sided lesion(s) with severe stenosis or regurgitation or intractable heart failure or very large vegetation (> 30 mm)[5]. In this case, antibiotic therapy was performed at first and clinical symptoms were relieved. However, the situation deteriorated rapidly on the 9th day as the fever came back and the vegetation and abscess were detected. It reminds clinicians that even if there are no indications for surgery for the time being, it is necessary to keep an eye out for changes of cardiac construction and function.

An already complex etiology of IE is further complicated by the appearance of comorbid abscesses and valvular perforations. In the present case, intraoperative monitoring revealed aortic valve perforation, presence of apothegmatic cystic spaces below the left coronary cusp of the aortic valve, and severe aortic valve regurgitation.

Surgical treatment involving valve repair and valve replacement, could get excellent outcomes for native valve endocarditis including lesions of either the aortic or the mitral valves[25-28]. However, there is little information concerning aortic valve repair in patients with culture-negative endocarditis. For this case, aortic valve repair was performed by using autologous pericardial patch plasty. A previous study demonstrated that the augmentation or partial replacement of defective aortic cusps with autologous pericardium is a safe and feasible surgical alternative, and further advocated that aortic regurgitation can be treated effectively by aortic valve repair using pericardial patch plasty[29]. Nevertheless, the reason for the enlarged echo range of the aortic valve lateral flap in the postoperative children is not clear, and whether the infection still exists or the cystic cavity is normal after the operation remains to be followed.

CONCLUSION

Collectively, our case report suggests tailored management of pediatric IE in children without predisposing factors. Further, for cases with persistent fever and abnormal

elevation of inflammatory factors (white blood cells and/or CRP), repeated blood cultures and color Doppler ultrasonography need to be performed to determine the most appropriate treatment option. Last but not least, we advocate that timely surgical intervention guided by serial echocardiography monitoring is crucial to prevent any further complications and enhance quick recovery.

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