CASE REPORT

Infective endocarditis in children with normal heart: Indication for surgical intervention

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Although infective endocarditis is an uncommon condition, it can be fatal if not treated. The new era of infective endocarditis in children with structurally normal heart has become apparent entity. Duke criteria has been established for a long time and gives clear guidelines for diagnosis; however, surgical indication in pediatric population needs to be tailored to individual patients.

Keywords: Endocarditis, Infective, Pediatric, Surgical management

1. Introduction

Infective endocarditis (IE) remains an uncommon life-threatening condition with an annual incidence rate ranging between 0.05 and 0.12 cases per 1000 pediatric admissions [1]. Prior to 1970s, majority of children with IE had underlying rheumatic heart disease. More recently, in the past two decades, congenital heart diseases (CHDs) have become the predominant underlying condition for IE in developed countries [1]. Furthermore, there has been an increase in the number of IE cases associated with CHD due to the increasing number of survived children with repaired or palliated CHD [1].

Although IE is uncommon in children with normally structured heart, it has been increasingly diagnosed in the absence of CHD [1]. The infection of endocardium under these circumstances

Disclosure: Authors have nothing to disclose with regard to commercial support.

Received 23 July 2018; revised 28 August 2018; accepted 12 November 2018.
Available online 22 November 2018

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URL: www.ksu.edu.sa
https://doi.org/10.1016/j.jsha.2018.11.003

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is often associated with indwelling central venous catheters near the heart or in association with immunosuppressed condition. Currently, it is estimated that 8–10% of pediatric IE cases develop in normally structured heart [1]. The management of IE depends mainly on prolonged antibiotics treatment as recommended by recently published guidelines [1]. The role of surgery in the management is limited to certain cases and indications [2].

While the diagnostic criteria and medical management of IE are well established, the role and indication for surgical intervention are not well defined. Due to limited number of sporadic cases, there are unlikely to be any randomized controlled trials for the treatment of IE in pediatric population, which posed a challenge for the writing group in compiling recommendations. Therefore, many of the current indications are based on consensus opinion [1]. In this report, we present a case series of IE in children with structurally normal heart who needed surgical management for IE. We discuss the indications and guidelines of surgical management of IE in children.

2. Case reports

2.1. Case 1

A 1-year-old female child was presented to the emergency department with a history of prolonged fever and poor feeding. The child was admitted to the pediatric medical ward for investigation. Her past medical history was significant for two recurrent infections; the first one was facial cellulitis and the second was septicemia. In her recent admission, blood cultures grew *Pseudomonas aeruginosa* that was treated with meropenem and gentamicin according to culture sensitivity and antibiogram. Because of the unusual history of recurrent serious infection, a screening echocardiogram (ECHO) was performed that showed normal cardiac anatomy with two intracardiac masses consistent with the diagnosis of endocarditis. The first mass measured 11 mm attached to the anterior leaflet of the tricuspid valve (TV; Fig. 1). The second mass measured 4.5 mm attached to the posterior leaflet of TV with mild tricuspid valve regurgitation (TR) and TR gradient of 25 mmHg. During the preceding 2 weeks following initiation of antimicrobial treatment for endocarditis, the patient was noted to be increasingly hypoxic, and repeated ECHO demonstrated detachment of large vegetation fragment and migration of one mass into the left pulmonary artery (LPA) with flow turbulence due to significant flow obstruction in spite of adequate antibiotics coverage and anticoagulation. As such, the patient was referred for surgical vegetectomy to release pulmonary flow obstruction. Vegetation was surgically excised from the TV and LPA. Tissue cultures from vegetation confirmed *P. aeruginosa* IE. The patient recovered after surgery with sterilization of blood and normal cardiac anatomy upon home discharge.

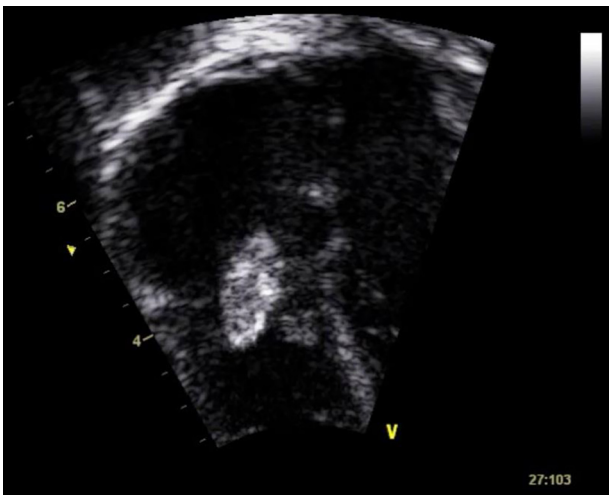

Figure 1. Echogenic mass passing through the tricuspid valve.

2.2. Case 2

A 3-month-old male infant was born full-term by normal vaginal delivery to a mother with gestational diabetes. The baby had profound hypoglycemia after birth and needed admission to neonatal intensive care unit (ICU) for blood sugar monitoring and intravenous glucose administration. The child needed high dextrose concentration to maintain normal blood sugar level; for this purpose, an umbilical venous catheter was inserted. Cardiac screening was performed initially which revealed hypertrophied Ventricular septum with no obstruction and otherwise normal heart structures. The child recovered and was discharged in good condition. After 1 month, he was readmitted to hospital with poor feeding and fever for 10 days. Complete blood count showed leukocytosis with white blood cell count of 23×10^3/mL and thrombocytopenia with platelet count of 24×10^3/mL. Blood and urine cultures were collected, and broad-spectrum antibiotics were initiated. Blood culture grew non-*albicans Candida* that called for initiation of intravenous amphotericin B therapy. Repeated blood cultures remained positive even after 1 week of antifungal treatment; meanwhile, an echocardiography showed large intra-atrial mass attached to TV with

no obstruction. Due to the large size of fungal mass with persistent fungemia that did not improve with systemic antifungal administration, the child was referred for surgical vegetectomy. A well-formed mass ($6 \times 4 \times 3$ cm) was excised from the right atrium (Fig. 2). The patient recovered after surgery with complete sterilization of blood with no residual cardiac lesion and was discharged in good condition.

2.3. Case 3

A 2-month-old male infant was born preterm at 34 weeks of gestation, with a birth weight of 2.1 kg. He had no major complications and required no mechanical ventilation or indwelling central venous catheter after birth. The baby was discharged home after a few days in nursery. One week after discharge, he became febrile at home with poor feeding and was readmitted to a peripheral hospital and was managed for neonatal sepsis. The blood culture grew *Candida albicans* for which intravenous amphotericin B was initiated. He continued to spike a fever despite adequate antifungal therapy; therefore, echocardiography was performed that showed a large mass at the junction of inferior vena cava and right atrium extending to the right ventricle through TV. The mass was 10–20 mm in size (Fig. 3). ECHO demonstrated no underlying heart disease.

He was then transferred to a tertiary hospital where a repeated serial echocardiography studies continued to show right atrium mass (Fig. 3) associated with persistent fungemia in spite of 30 days of combined antifungal treatment with amphotericin B and fluconazole. The blood cultures were consistently growing *C. albicans* and a repeated echocardiography showed no decrease in the mass size with right atrioventricular inflow obstruction. The patient was then taken for surgery, and the right atrial mass was surgically excised. Histopathology of the mass showed *C. albicans*. Postsurgical echocardiography showed no residual mass, and the patient received amphotericin B for 6 weeks with complete sterilization of blood after vegetectomy. No recurrent mass was seen in the follow-up echocardiographs, and no residual cardiac lesion was observed.

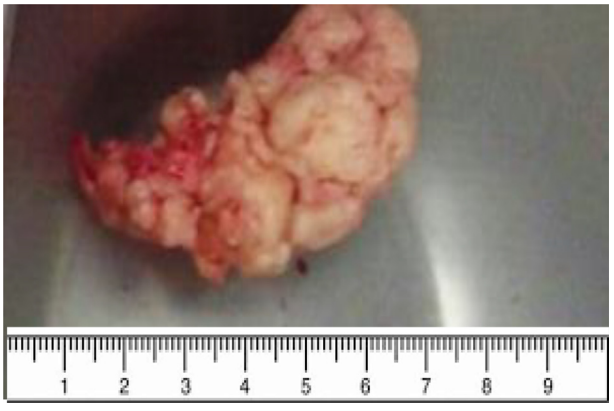

Figure 2. Well-formed mass was excised from his right atrium. Tissue cultures confirmed non-albicans Candida vegetation.

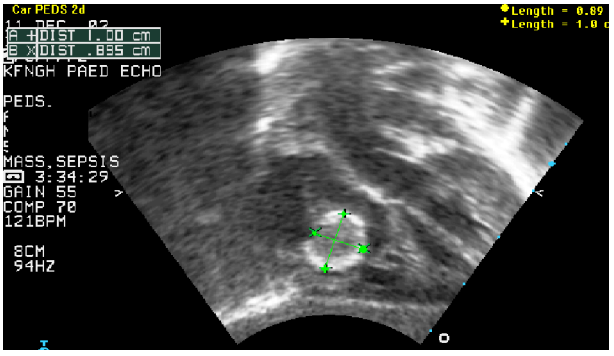

Figure 3. Fungal mass in the right atrium of a 2-month-old infant.

3. Discussion

IE is an uncommon condition in pediatric patients with potential serious consequences. The complex nature of this disease demands accurate diagnosis and promotes treatment [3]. While pre-existing heart disease is the main predisposing factor for pediatric IE, cases of IE without underlying heart disease have been increasingly reported [4].

Data on IE in children with structurally normal hearts and no predisposing factors are limited. Russell et al. [3], in their 21 years of review of surgical outcome of IE, found that 35 cases of endocarditis needed surgical intervention; of these, 14 (40%) had no underlying congenital heart defect. In addition to the growing number of children surviving following cardiac surgery, there are other risk factors considered as predisposing conditions for IE. In one study, the authors highlighted that improvement of resuscitation methods, newer technologies, and more invasive devices used in neonatal and pediatric critical patients have all created a new group of patients with an increased risk of endocarditis [5]. Currently, approximately 8–10% of pediatric IE cases developed without having abnormally structural heart although other underlying risk factors can be identified such as immunodeficiency, chronic parenteral nutrition, and those with central venous catheters near the heart or tunneled central venous catheters [1]. Carceller et al. [5], in

their study about the trend in pediatric IE, found that 15 out of 56 (26%) endocarditis patients had serious systemic underlying disease without congenital heart problem, while six out of these 56 (7%) were completely healthy children.

There are some differences in the characteristics of IE between children with normal heart and those with abnormal heart. Microorganisms causing endocarditis in children with normal heart may differ from those causing IE in children with abnormal heart. In their recent report published in 2015, European heart group highlighted two new subgroups of patients with IE: the first subgroup includes patients in the ICU and the other includes patients with IE affecting the right side of the heart. Both subgroups had no underlying CHD, but they might have had other risk factors and different spectrum of causative organisms. In ICUs, *Staphylococci*, *Streptococci*, and fungi are common causative microorganisms for IE, whereas gram-negative bacilli are also encountered frequently in pediatric ICUs [1,2]. Right-sided endocarditis can occur when there are intravenous catheters; therefore, microorganisms carried by the bloodstream enter the right side of the heart, potentially causing IE on pre-existing nonbacterial thrombotic endocarditis which is caused by central catheter and serves as an excellent nidus for subsequent bacterial or fungal colonization in a patient with bacteremia or fungemia [1]. Two out of our three cases had opportunistic organisms related to health care environment during their ICU admission

Signs and symptoms of IE may be vague especially in neonates and small infants who do not show the typical picture of Duke criteria [6]. That makes diagnosis of IE in this group of patients a challenging task, needing a high index of suspicion. Another dilemma regarding the management is the initiation of broad-spectrum antibiotics early upon diagnosis and then adjustment and narrowing down the selection of antibiotics based on culture results and antibiogram. It is known that the treatment of bacterial IE requires 4–6 weeks of antibiotics. The duration needed may be even longer in cases of fungal endocarditis. Surgical indications and timing of surgery in IE are subjects of debate [7]. It is important to consider early intervention in active IE to avoid progression to acute intractable heart failure, irreversible structural damage, persistent source for bacteremia and systemic infectious thromboembolic phenomena [7].

In 2015, the European Society of Cardiology published guidelines on the prevention and treatment of IE [2]. The indications for surgery in these guidelines closely resemble the American College of Cardiology / American Heart Association guidelines of 2015 [1]. More recently, in 2016, the American Association for Thoracic Surgery published executive summary of surgical indications for IE that include valve dysfunction resulting in symptoms of heart failure, left-sided IE caused by *Staphylococcus aureus*, fungal, or other highly resistant microorganisms, IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions, evidence of persistent infection 5–7 days after initiation of appropriate antibiotic therapy [8].

Our two cases have different organisms, both of them reported as common organisms of IE in native heart. Fungal endocarditis in children is usually caused by *Candida* species. With the increasing use of central venous catheter in infants and children and infusions of high glucose concentrations and hyper alimentation, *Candida* infections of the mural or valvular endocardium have occasionally been recognized. Fungal endocarditis is often associated with large friable vegetation. Fragmentation of vegetation and showering systemic infected thrombi from vegetation may produce serious local or extracardiac complications, such as progressive valvular dysfunction, myocardial dysfunction, and periannular extension of infection with local abscess formation. Extracardiac complications, such as neurological squeal, stroke, and embolization, may also occur. European guidelines recommended amphotericin B with or without flucytosine or echinocandin at a high dose; however, they did not specify the duration of treatment advised for long-term suppressive therapy with oral fluconazole, whereas American guidelines mentioned long-term suppression therapy for only those cases which did not undergo cardiac surgery [1]. With the exception of neonates with mural endocarditis and occasionally older children, medical therapy of fungal IE is usually unsuccessful, and surgery in conjunction with antifungal agents is required [1].

Our first case was complicated with LPA obstruction after initial regression of TV mass with antibiotic administration. However, a large fragment was detached and embolized into LPA leading to significant obstruction. Embolic complications may occur in 30% of cases [1]. Numerous studies in adults have shown increased risk for embolization when vegetation exceeds 10 mm, thereby indicating a role for early surgical intervention in those cases with such large

vegetation. Recently, this finding was supported in a pediatric study [1]. The indications for surgical removal based on the size of mass remain a subject of controversy in premature infants with a low body weight. The location of the vegetation may also be a risk factor. Left-sided lesions are considered a risk for systemic embolization. Particular organisms namely *Staphylococci*, *Pneumococci*, and fungi also carry a higher risk for embolization [1].

Pulmonary embolism is a serious complication in right ventricle IE. Hejna et al. [9] reported an adult case of intravenous drug user who had a sudden death, and postmortem examination showed complete destruction of the anterior and septal cusps of TV and yellow mass with a slightly granular surface that was wedged into both branches of the pulmonary artery, causing complete obstruction similar to saddle pulmonary embolism.

Numerous pulmonary infarcts resulting from small emboli may be associated with right-sided bacterial endocarditis. Mansour et al. [10] reported regarding an 11-year-old child who had IE complicated with small septic pulmonary emboli originating from the tricuspid vegetation. Pulmonary emboli were diagnosed by computed tomography after 25 days of initiating antibiotic and needed no surgical treatment. Nonetheless, another study reported regarding a 4-year-old girl who had ventricular septal defect and received corticosteroid to treat her autoimmune hemolytic anemia; she further demonstrated signs of EI with vegetation distending from TV to pulmonary valve causing stenosis and regurgitation of pulmonary valve. She underwent surgical resection but had postsurgical recurrence, leading to massive pulmonary embolism and death [11].

Both European and American guidelines did not include the risk of embolization in indications for surgery, and the European group mentioned that the exact role of early surgery in preventing embolic events remains controversial [2]. Some indications for urgent surgery to prevent embolization include left-sided lesion with severe stenosis or regurgitation or intractable heart failure or very large vegetation of >30 mm.

Although our first case had large vegetation (>10 mm), we initially opted to wait for surgery and to give more time for medical treatment as we noted some early regression in size with the initiation of antibiotics. However, embolization into pulmonary artery happened during regression in size, and the patient had desaturation with significant obstruction of LPA by large vegetation that demanded immediate surgical extraction.

Currently, in the absence of pediatric evidence-based data that favor prophylactic surgery for the prevention of primary thromboembolic events, decision of health care providers is difficult and individualized. Prediction of an individual patient's risk for embolization remains challenging with conflicting data published regarding the specific value of echocardiographic determination of vegetation size or specific location as predictors [1,2].

In the second case, the decision was taken early within 2 weeks of patient admission, keeping in mind the natural history of fungal endocarditis and difficulty to clear it by medical treatment only. Furthermore, in the third case, it took a longer period to go for a surgical intervention mainly due to the patient's size and treatment occurring in a peripheral hospital. Eventually, a surgical intervention was decided when hemodynamic effects started to appear with evidence of inflow obstruction and absence of regression in size in the presence of persistent candidemia.

Although Shamszad et al. [12] mentioned that the lesions that are located in the left-sided heart were the most that needed surgical intervention, in all our three cases, the right-sided heart was the affected site.

IE is a disease that needs a collaborative approach. European guidelines established criteria to transfer the patient to an ''endocarditis team'' [2]. Early consultations with infectious disease, cardiology, and cardiac surgery services are recommended for these patients. It is also important to define the patient populations that are at higher risk for IE or its complications. Several factors predispose children with IE to potentially life-threatening complications that may require early surgery [1].

The currently published recommendations for surgical management of pediatric IE are mostly extrapolated from adult experience. Indications for cardiovascular surgery in pediatric IE are sometime clear. However, in many cases, indications should be evaluated individually on a case-by-case basis.

4. Conclusion

Pediatric IE in children without predisposing factors differs significantly from the usual IE in children with abnormal heart. Due to the acute and complicated course, high awareness among pediatricians and prompt diagnosis are crucial. Appropriate medical management may require

early surgical management to prevent complications and enhance fast recovery.

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