Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.60, No.3(2020). p.167-72; doi: http://dx.doi.org/10.14238/pi60.3.2020.167-72

Case Report

Pediatric infective endocarditis initially presenting as hemorrhagic stroke

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Infective endocarditis refers to infection of the heart valves. While its incidence is low, it may cause serious complications. Despite advances in its management and diagnosis, this condition still retains high mortality and significant morbidity. Considerable controversy remains regarding antimicrobial prophylaxis to prevent infective endocarditis in patients with congenital heart disease. Neurologic complications are the second most common complication in patients with infective endocarditis, occurring in approximately 33% of cases.[1] These include encephalopathy, meningitis, stroke, brain abscess, cerebral hemorrhage, and seizures. The vegetation formed as a consequence of endocarditis may dislodge and cause embolization. Vegetation size alone is an unreliable marker for embolization risk, however, size, in addition to location, mobility, infecting agent, and presence of antiphospholipid antibodies have the potential to be prognostic markers. The brain is the most frequent site of embolization. Furthermore, advances in medical approaches have resulted in an increase of patients at risk of endocarditis due to the now common and widely available indwelling intravascular approaches in medicine. In this report, we present a case of infective endocarditis in a child first presenting with hemorrhagic stroke.[1,2] **[Paediatr Indones. 2020;60:166-71; doi: http://dx.doi.org/10.14238/pi60.3.2020.166-71].**

Keywords: *endocarditis; aneurysm; stroke*

The Case

A six-year-old Indonesian boy was referred to our facility with a history of persistent fever that had lasted for two weeks. He had recently been diagnosed with ventricular septal defect, as well as tricuspid, mitral, aortic, and pulmonary regurgitation. The child was being followed up while awaiting surgical correction. Two weeks prior to the current admission, he had been admitted to the hospital with a diagnosis of hemorrhagic stroke. He presented with left-sided hemiparesis with motoric strength of 1/5. Multi-slice computed tomography (MSCT) revealed an intracerebral hemorrhage at the right parietal lobe and an adjacent hyperdense lesion. The patient was treated conservatively and subsequently discharged, but he developed a fever at home. His parents denied any history of illnesses in the family. At the time of presentation to our facility, he was afebrile with stable blood pressure. Glasgow coma scale (GCS) at

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Submitted June 8, 2018. Accepted April 28, 2020.

presentation was E4V5M6. Physical examination was significant for a heart rate of 150 beats per minute (bpm) and a grade 3/6 pansystolic murmur at the left lower sternal border. The remaining physical examination findings were within normal limits. Neurological examination revealed a left-sided hemiparesis with motor strength of 3/5 (improved compared to 2 weeks prior) and a positive Babinski reflex. It was concluded that this was a residual neurological deficit. To confirm the diagnosis of a mycotic aneurysm, MSCT and computed tomography (CT) angiography were done. The MSCT and CT angiography showed an intracerebral hemorrhage in the right parietal lobe with an adjacent hyperdense lesion, indicative of a mycotic aneurysm. CT angiography also revealed a mycotic aneurysm adjacent to the periphery of the right middle cerebral artery.

Electrocardiography showed the Katz-Wachtel phenomenon (large biphasic QRS complex in leads V2 to V5) suggestive of biventricular hypertrophy. Peripheral blood count revealed anemia (hemoglobin level 8.1 mg/dL and hematocrit 24 vol%) and an elevated erythrocyte sedimentation rate (53 mm/hour). Rheumatoid factor was positive. A chest X-ray showed an upward-pointing apex and a plethora within both lung fields. Echocardiography showed a perimembranous ventricular septal defect (VSD) 4 mm in diameter, with a trans-VSD gradient of 68 mmHg. Mild tricuspid regurgitation, mild mitral regurgitation, moderate aortic regurgitation, and mild pulmonic regurgitation were also present (**Figure 1**). Vegetations were seen on the anterior mitral leaflet with a dimension of 7-9 x 5-6 mm, on the right coronary cusp with a dimension of 6x8 mm, and on the pulmonary valve with a dimension of 6x7 mm (**Figure 2**). Blood culture using a specimen taken prior to the administration of antimicrobials was negative.

We diagnosed the patient with infective endocarditis and administered a treatment regimen of 1.5 g of intravenous (IV) ceftriaxone once daily, 45 mg IV gentamicin once daily, 6.25 mg IV captopril twice daily, 5 mg oral furosemide twice daily, and 6.25 mg oral Aldactone once daily. Repeat echocardiography done 22 days after initial presentation showed reductions in vegetation size to 4x6 mm on the mitral valve, 2.3x3.1 mm on the pulmonary valve, and 3x5 mm on the right coronary cusp. At the time of presentation, no acute management for stroke was undertaken since only residual deficits remained. The patient was scheduled for rehabilitation after the infective endocarditis (IE) was treated. The patient's clinical course is summarized in **Table 1**.

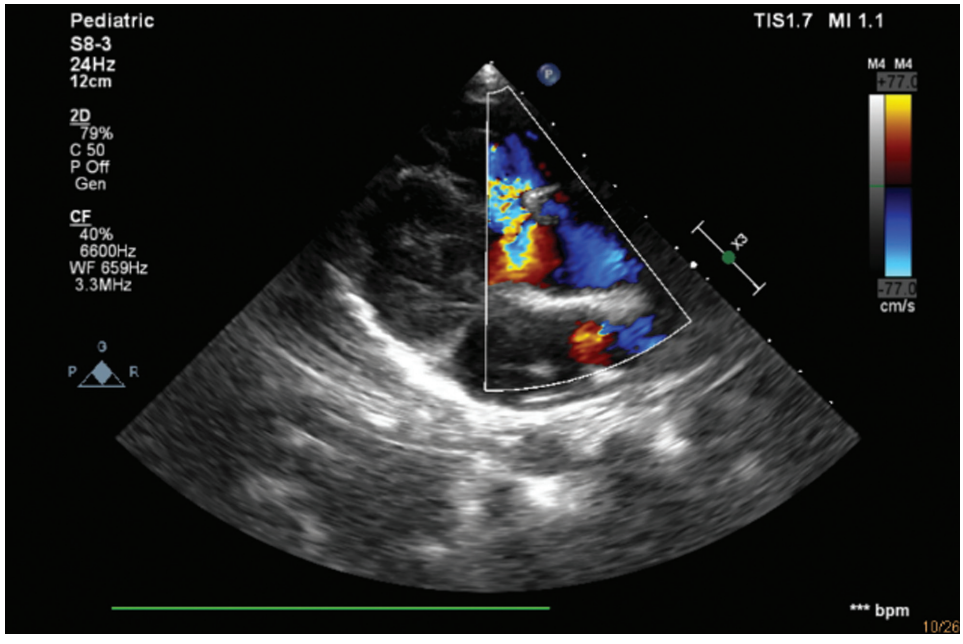

Figure 1. Transthoracic echocardiography with Doppler mode showing tricuspid valve regurgitation

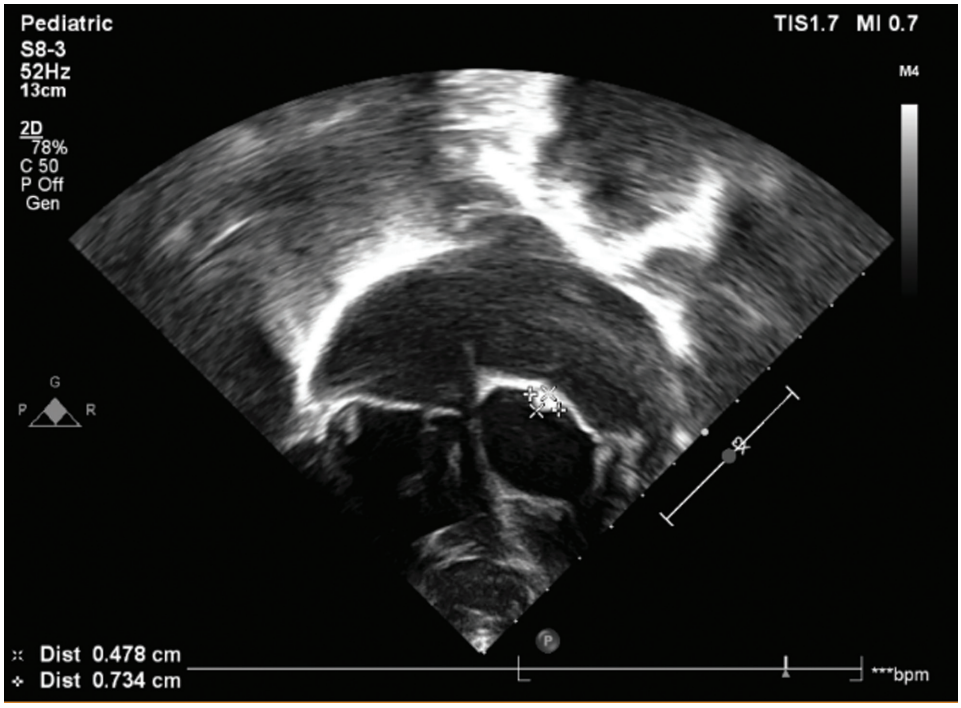

Figure 2. Transthoracic echocardiography showing vegetation on the mitral valve

Table 1. Timeline summary of the patient's progression

Chronology	Progression
One month prior	Diagnosis of VSD, TR, MR, AR, and PR was made
Two weeks prior	Hemorrhagic stroke; experienced fever after discharge
On admission	Infective endocarditis, confirmation of previous CHD diagnosis, residual hemorrhagic stroke, and confirmation of mycotic aneurysm
22 days after admission	Repeat echocardiography showed reductions in vegetation sizes

AR=aortic regurgitation, CHD=congenital heart disease, MR=mitral regurgitation, TR=tricuspid regurgitation, VSD=ventricular septal defect, PR=pulmonary regurgitation

Discussion

The pathogenesis of IE is multifactorial and is the result of complex interactions between bloodstream pathogens, matrix molecules, and platelets at sites of endocardial cell damage.[3] Furthermore, a substantial portion of the disease's clinical manifestations arises from the host's immune response to the infecting microorganisms.[3]

Difference in pressure of chambers of the heart causes turbulence in blood flow, which will inturn predispose to the occurrence in non-bacterial thrombotic endocarditis (NBTE). This turbulence causes trauma in the endothelial and valvular tissues, which will generate platelet and fibrin deposition and finally result in NBTE. This accumulation of platelet and fibrin, in the presence of bacteremia, will be colonized by circulating bacterias and will result in IE.[3]

As mentioned, bacteremia occurs in the pathogenesis of IE. These microbes may originate from sites such as mucosal surfaces, gingival crevices arounnd the teeth, the oropharynx, GI tract, urethra, and vagina.[3] The occurrence of trauma to these sites can release a variety of microbial species transiently into the bloodstream. Transient bacteremia caused by viridans-group streptococci and other oral microflora commonly occur in association with dental extractions

or other dental procedures or with routine daily activities such as toothbrushing.[3] The frequency and intensity of the resulting bacteremia are believed to be related to the nature and magnitude of the tissue trauma. Also, the microbial species entering the circulation depend on the unique endogenous microflora that colonizes the particular traumatized site.[3] Microbiological diagnosis is the most important step in managing IE. In 1 to 2.5% of all IE cases, no microorganisms are isolated in blood cultures, leading to delayed diagnosis and treatment, as well as significant effects on clinical outcomes.[4]

The clinical presentation of this condition has also changed.[5] With the ever-increasing use of antibiotics, the classic IE presentation is generally no longer in the initial findings of patients with the disease. Although far less frequently seen nowadays, classical findings of IE such as Janeway lesions and Roth spots could still be invaluable clues leading to earlier treatment.[5]

Advances in health care delivery have raised the concern of antimicrobial resistance, and the resulting altered epidemiology of infective endocarditis.[6] Methicillin-resistant *Staphylococcus aureus* (MRSA) has been encountered internationally as a relatively common cause of IE, with patients having the distinctive characteristic of persistent bacteremia.6 Despite a higher rate of persistent bacteremia, there is not much difference in mortality between MRSA- and methicillin-sensitive Staphylococcus aureus (MSSA)-infected patients.[6] This finding is believed to be due to the overall high mortality of *S. aureus* IE (regardless of the antimicrobial resistance profile of the infecting pathogen). It is important to note that approximately 20% of patients with MRSA IE developed their infection in the absence of identifiable health care contact.[6]

The differential diagnosis and evaluation of acute stroke in the pediatric population should be based on the understanding that the probability of a non-atherosclerotic etiology is much higher than the adult population.[7] Thus, it is prudent to be aware of the broad and appropriate differential diagnoses for pediatric patients who present with acute ischemic stroke.[7]

Transthoracic echocardiography (TTE) remains an indispensable tool for the diagnosis of IE. Transesophageal echocardiography (TEE), however, remains more sensitive in detecting lesions <1 mm in size.[8] It also poses as an alternative in patients using multiple devices on the chest, such as in intensive care units. However, TTE remains the simplest approach compared to TEE.[9] Anterior mitral leaflet (AML) vegetations remain one of the most common echocardiographic findings in relation to IE, as we noted in our patient.[8,9]

An infectious cerebral aneurysm in IE patients suggests that vascular tissue is friable and vulnerable.[10] Intracranial aneurysm arises from either septic embolism of the vasa vasorum or from subsequent bacterial dissemination spreading from a septic embolism of occluded vessels. Infectious aneurysms can be formed anywhere in the brain arteries, but the distal branches of the middle cerebral artery are the most commonly susceptible, consistent with the findings in our patient.[10] Clinical symptoms are highly variable and include neurological disturbance, headache, confusion, and seizures.[11]

Studies have shown that at least 50% of intracranial aneurysms due to infection decrease in size and are eliminated by the administration of effective antibiotics.[10] Appropriate antibiotic treatment is mandatory for all patients with infectious intracranial aneurysms.[10] Some cases exhibit enlargement of vegetation size despite ongoing antimicrobial therapy of the infection, hence, repeated evaluation using MR and CT angiography is of utmost importance. A Japanese study showed that MRI was superior to CT.[12]

A study of intracranial infected aneurysms complicating endocarditis found that the most significant factor for treatment consideration was whether an aneurysm had ruptured.[13] Treatment-related mortality was higher in patients with ruptured aneurysms than in patients with unruptured aneurysms (24 *vs.* 9%)[13] Among patients with ruptured aneurysms, mortality was higher in those treated with antibiotics alone compared with those treated with both antibiotics and surgery (49 *vs.* 12%).[13] Unruptured mycotic aneurysms are generally treated with antibiotics alone, however, whenever possible, ruptured aneurysms should be managed with a combination of antibiotics and surgery.[14] Endovascular approaches are increasingly being used in such cases.[14]

Our suspicion of infective endocarditis was based on our patient's prolonged fever in the face of

congenital heart disease. He had also been diagnosed with hemorrhagic stroke 2 weeks prior, and at his presentation, the neurological deficits had improved, so he required no immediate post-stroke management. We decided to further explore the cause of the fever by performing CT angiography, which confirmed the mycotic aneurysm.

Our patient's blood culture result was negative. It is important to consider that 2 to 7% of all pediatric IE cases have negative blood cultures, similar to adult cases.[15,16] However, to be declared "blood culture-negative infective endocarditis," the patient must meet the condition of negative cultures from inoculation of at least three independent blood samples in a standard blood culture system, after five days of incubation and subculturing.[17,18] In IE with negative cultures, one must consider an indolent organism or a fungal cause.[17] However, since our patient improved as shown by the reductions in vegetation sizes, it was unlikely that such atypical organisms were the cause. A limitation of this conclusion is that we made only a single attempt to culture blood from our patients.

Ceftriaxone and gentamicin were chosen as the empiric antimicrobial regimen for our patients. Ceftriaxone has good coverage of both Gram-positive and negative organisms; gentamicin covers mostly Gram-negative organisms.[10,11] Most recent IE infections are caused by methicillin-resistant Staphylococcus aureus, with the incidence of MSSA in IE on the rise.[19] The infective endocarditis in our patients did not require surgery. Closure of the VSD was planned after recovery from endocarditis. Post-endocarditis evaluation of the valves and VSD anatomy by echocardiography will be done before deciding on VSD closure by surgery or occlusion.

We acknowledge that current recommendations regarding empirical antimicrobial regiment in treating infective endocarditis mandate the use of vancomycin and gentamycin as the initial empirical antimicrobial agents of choice. However, difficulty in procuring vancomycin resulted in ceftriaxone being chosen as an empirical agent in this case. We suspected that the presence of congenital heart malformation in our patient may have been the inciting factor for the presumed bacterial infection.

The reported IE incidence rates in the children with congenital heart disease range from 40 to 60 per 100,000 person-years, which is several times higher than in general pediatric populations.[20] In these studies, ventricular septal defects put patients at higher risk for developing infective endocarditis, as seen in our patient. Other risk factors include cardiac surgery within six months and age <3 years.[20,21]

In conclusion, hemorrhagic stroke is a rare, initial presentation of pediatric infective endocarditis. Neurologic involvement, such as mycotic aneurysm and hemorrhage, should be considered as a presenting manifestation of infective endocarditis, irrespective of cardiac malformation. Early recognition and intervention will hopefully decrease morbidity. A broad but appropriate range of differential diagnoses should be considered in pediatric patients who present with stroke.

Conflict of Interest

None declared.

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