Infective Endocarditis Associated with Multisystem Inflammatory Syndrome in Children (MIS-C): Two Case Studies

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ABSTRACT

Infective endocarditis (IE) is the infection of endocardial surface of the heart. IE is the rare disease with significant complications which require early diagnosis and proper treatment for reducing morbidity and mortality.IE with vegetation on pulmonary valve, leaflets are uncommon. However, we have diagnosed one case with infective endocarditis associated with Multisystem Inflammatory Syndrome in Children (MIS-C) which is related with COVID-19. MIS-C is commonly associated with coronary artery aneurysm (CAA), myocarditis and heart failure. Our patient had IE and was subsequently affected with MIS-C due to COVID. The child had vegetation on pulmonary valve with flail pulmonary valve-leaflet with grade II pulmonary regurgitation and MIS-C related CAA. The second child was previously diagnosed as infective endocarditis and was treated in other hospital for intravenous antibiotic for four weeks. However, in our hospital he was diagnosed clinically, by laboratory investigations and by echocardiography as MIS-C with large vegetation, which was surgically removed, and biopsy revealed mycobacterium tuberculosis as causative organism.

Key words: *: Infective Endocarditis, Vegetation on pulmonary COVID-19, MIS-C, Coronary Artery Aneurysm (CAA).*

INTRODUCTION

Infective endocarditis (IE) is an infection of the endocardium, which is caused by various types of microbial infections. Although this entity is less common, IE can lead to significant consequences like injury to endocardium, vascular intima or valve, formation of nonbacterial thrombotic endocarditis (NBTE), transient bacteremia, adherence of the bacteria or organism to the NBTE and subsequent rapid multiplication of buried microorganism within a vegetation. Early diagnosis, appropriate intervention and management can have a greater positive impact on reducing IE related morbidity and mortality. In this case study, we present two cases with infective endocarditis associated with Multisystem Inflammatory Syndrome in Children (MIS-C) which was related to COVID-19 and has been successfully managed in this hospital.

CASE SUMMARY 1

A 2 year 3-month-old baby boy weighing 12 kg, height 91 cm, first issue of consanguineous parents was admitted in EHD with the complaints of fever for 7 days, highest peak of temperature was 104°F associated with poor feeding and irritability. The baby was at home and treated with paracetamol. The child had four episodes of continuous fever (max 104 ˚F) within last three months with prolonged duration (10 to 15 days) during this COVID-19 pandemic. His fever was continuous and for this he was admitted in outside hospital and was empirically treated with antibiotic inj. Ceftriaxone & inj. Amikacin followed by oral cefixime for 3 days. He had gross noncompliance with injectable antibiotics. However, he had no history of cough and cold or history of contact with COVID-19 positive . patient and febrile illness in other family members On admission in our hospital baby was ill looking, irritable, afebrile, moderately pale with tachypnea (40 b/min), tachycardia (170 beat/min), normal blood pressure (BP was 90/60 mmHg on 50th centile), SPO2 98% on room air, coated tongue, pedal oedema. He also had neck rigidity with positive kernig sign. Skin survey normal, no rash, no lymphadenopathy. His lungs were clear, heart S1, S2 present with an early diastolic murmur present in left second grade 3/6. All jerks were intact and planter bilateral flexor.

On admission his lab investigations showed low HB (7.3 gm/dl), TC 8.06 × 10 9/L, N-67 %, thrombocytopenia (platelet 110 × 10 9L/ m3) with microcytic hypochromic anemia, high CRP(27.09mg/dl; normal < 0.5), high D dimer (15818 µg/ L; normal : < 500), S. Ferritin (427 ng/ml; normal :12-140), hypoalbuminemia (S. albumin 1.8 mg/dl), chest X ray showed opacity in right sided lung. He had RT PCR for COVID- 19 negative but COVID antibody positive. His 2D and color Doppler echocardiography revealed vegetation (4.5mm×4.4 mm) over the pulmonary valve. Thickened distorted pulmonary valve with flail leaflets with grade II pulmonary regurgitation, no pulmonary stenosis. Small aneurysmal dilation of left anterior descending artery (LAD) and right coronary artery (RCA). Dilated left main coronary artery (LMCA), LAD 3mm (Z score +4.3; normal 0.87 to 2.2 mm), RCA 3.4mm (Z score + 4.41; normal 1.00 to 2.48 mm), LMCA 2.8 mm (Z score + 2.2; normal 1.27 to 2.71 mm) ,mild pulmonary arterial hypertension,

good biventricular function.Four samples of blood culture and sensitivity (C/S) were sent on different time according to Modified Duke Criteria 2. Blood C/S revealed staph aureus sensitive to vancomycin. CSF study was normal. Urine routine examination and C/S were normal. His dengue NS1, ICT for malaria were negative and widal test was normal. His MRI of brain revealed normal study. We started inj meropenem, vancomycin and methylprednisolone (1 mg/kg/dose 12 hourly). Packed RBC was given. on second day of admission, the child developed shivering followed by cyanosis on lips and finger, SPO2 was 96% in room air with low blood pressure. After the patient was settled, Intravenous Immune Globulin (IVIG) was given at a dose of 2gm/kg. His fever subsided within 24 hours of IVIG infusion. He was also given inj. methylprednisolone for successive six days. Then oral prednisolone started on the seventh day. Gradually the dose tapered over 4 weeks.

Repeat echocardiography was done on 8th day of admission which revealed one vegetation on pulmonary valve (2.4mm x2.2 mm) reduced in size, distorted thickened pulmonary valve with flail leaflets, moderate to severe pulmonary regurgitation, dilated left descending artery. Follow up echocardiography confirmed reduction of the size of vegetation within two weeks of treatment. At 5th week of treatment, we reported the disappearance of vegetation. Notwithstanding the permanent damage to pulmonary valve caused free pulmonary valve regurgitation. The parents were counselled regarding further follow-up.

CASE SUMMARY 2

A 3 year 6-month-old boy weighing 12 kg, height 91.5 cm, 4th issue admitted through OPD, EHD with the complaints of high grade, irregular fever for last 4 months. Highest recorded temp was 102° F and fever subsided by taking paracetamol. Fever was associated with itchy erythematous rash over both upper and lower limbs for the last several months. He was a diagnosed case of congenital mild pulmonary valve stenosis. He had history of infective endocarditis (vegetation on pulmonary valve) which was treated with antibiotics and antifungal for four months (10.06.19 to 08.09.2019). Boy had recent history of contact with COVID-19 positive patient in family.

On admission baby was afebrile, SPO2 98% in room air, respiratory rate 24 breath/min, heart rate 120 b/min, BP 100/60 mmHg, mildly pale, no lymphadenopathy, and chest deformity present. His weight for age and height for age was below 3rd centile. Skin survey revealed follicular hyperkeratosis in both lower limbs.Precordium examination revealed deformed chest with normal findings. Abdominal examination revealed hepatomegaly (2.5cm). On admission lab investigation revealed microcytic hypochromic anemia. There was also high D-dimer, high ferritin and low vit. D level. He tested Positive for RT-PCR for COVID.

2D and color Doppler echocardiography showed one large (25mm x14mm) irregular, echogenic, homogenous, oscillating mass (vegetation) moving along blood flow from Right Ventricular outflow tract (RVOT) to pulmonary artery through pulmonary valve during systole and diastole. Stalk is attached above pulmonary valve. Mild pulmonary valvular stenosis (14 mmHg) and small aneurysmal dilatation of LMCA and RCA with dilated LMCA with normal cardiac function. Chest X ray revealed right sided enlarged radiolucent area (? Calcified hilar lymph node). CT pulmonary angiogram dilated main pulmonary artery (MPA) measuring 2.3 cm, right pulmonary artery (RPA) 1.5 cm and left pulmonary artery (LPA) 1.3 cm. A soft tissue structure measuring about 2.7x1.2 cm was noted at the root of the main pulmonary artery, compressing semilunar valve towards left which is the movable during systolic and diastolic phases. Calcification (1.4 x 1.0 cm) noted in right hilar region.

After admission he was treated with IVIG 2gm/kg over 24 hours, inj. ceftriaxone, inj vancomycin, inj gentamycin after sending aerobic blood culture of 5 samples from 5 different sites over 24 hours. Later on, low dose tab aspirin was added. As second blood culture showed Staphylococcus Saphrophyticus which was sensitive to inj gentamycin and inj vancomycin, we continued the same antibiotics. Subsequently, Patient underwent surgery to remove the vegetation and biopsy revealed Mycobacterium tuberculosis. We started anti TB drugs along with other medications.

DISCUSSION

Infective endocarditis is the infection of endocardium caused by different types of microbial infection[1]. Although the prevalence of IE is lesser than the congenital heart diseases, the consequences of IE are

life threatening. The population are at risk group for IE with underlying congenital structural heart diseases with jet flow through shunt or defective valve, post-surgical interventions and indwelling central venous catheter or prolonged use of venous line for intravenous medications due to frequent hospitalization. Damage to endocardium, vascular intima or valve, formation of nonbacterial thrombotic endocarditis (NBTE), transient bacteremia, adherence of the bacteria or organism to the NBTE and subsequent rapid multiplication of buried microorganism within a vegetation is the sequence of events, which occur because of complex interaction between microorganism and usual host immune response. Vegetation may cause valvular damage followed by dysfunction and shedding of vegetation itself can cause embolism as well as ischemia, and necrosis in important tissues and organs, resulting in high mortality rate[2].

Our first child had several episodes of high spiking temperature for last three months and was treated for ten to twelve days each time in a hospital with intravenous antibiotic as a probable case of enteric fever nevertheless his widal test and blood culture were negative. His compliance with antibiotics were poor. During last episode of fever after admission in our hospital his blood culture sensitivity test, triple antigen, serological test for dengue and Kala-Azar were negative. Because of his high fever with irritability and neck rigidity, he was evaluated for tubercular meningitis (TB gold, CSF study, brain MRI) which were normal.The child had spiking fever (104 ° F) for more than one week. The child had hepatosplenomegaly with pneumonitis in chest x-ray and neutrophilic leukocytosis, high CRP, high D-dimer suggested for 2 D and color Doppler echocardiography for exclusion of MIS-C (Multisystem Inflammatory syndrome in Children). However, he had small aneurysmal dilation of LAD (Left anterior Descending artery) and RCA (Right coronary artery) and dilated LMCA (Left main coronary artery) as shown in Fig 1, Fig 2. In addition, he had one non-obstructive small vegetation attached on pulmonary valve leaflet (Fig-3). Pulmonary valve leaflets were thickened distorted and flail which caused severe pulmonary regurgitation (Fig 4). Pulmonary regurgitation of the infected valve was nosis as MIS-C. almost constant and results from a various mechanism.

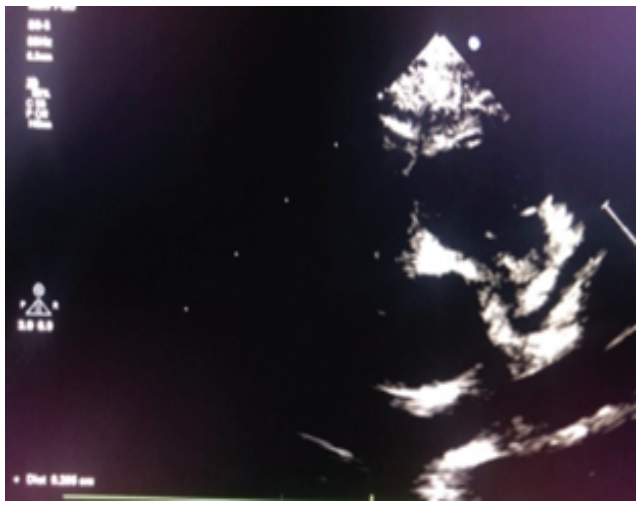

Fig 1 (case1) : Left anterior descending artery (LAD)aneurysm with small vegetation on pulmonary valve.

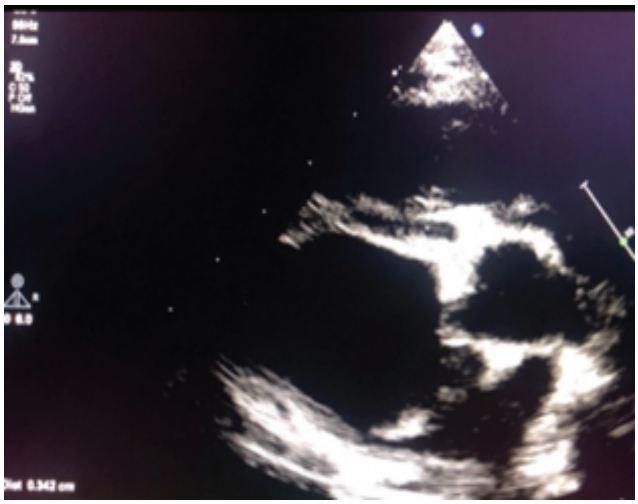

Fig 2 (case1): Aneurysmal dilation of right coronary artery (RCA).

Such as for the destruction of pulmonary valve leaflets and their noncoaptation due to adhesion of vegetation, itself on pulmonary valve leaflets extending to the tip. Although RT-PCR for COVID-19 was negative, his positive antibody for COVID-19 emphasized the diag Evangelista et al described in their study valvular regurgitation because of vegetation which also described variety of dysfunction of valve such as noncoaptation, perforation, to complete flail leaflets. They even described valvular perforation leading to severe valvular insufficiency that may cause the acute onset of heart failure[3].Although our child had no signs of heart failure because of timely diagnosis and treatment.

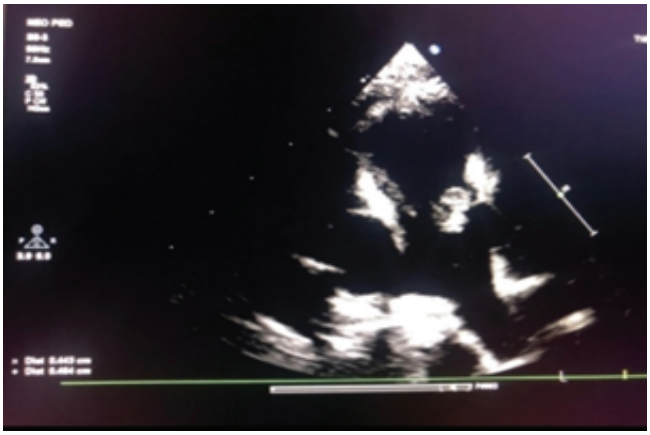

Fig3 (case 1): Small vegetation on pulmonary valve.

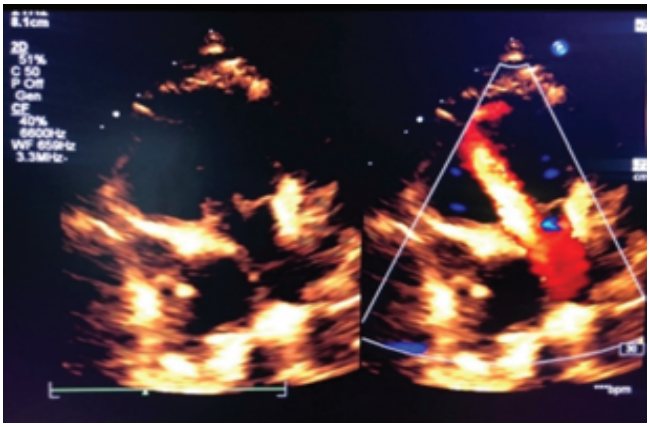

Fig 4 (case 1): Severe pulmonary valve regurgitation through damaged valve.

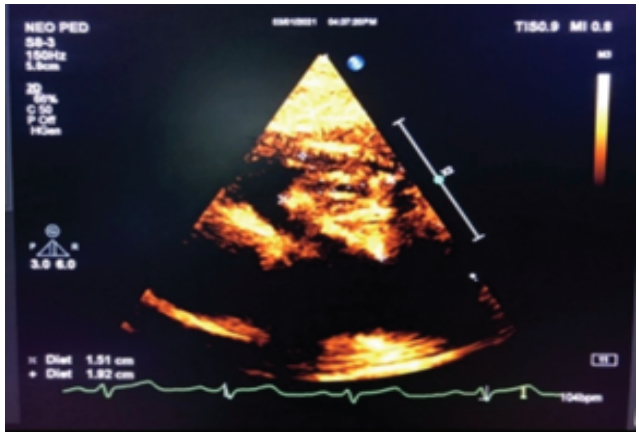

Fig 5 (case 2): Large vegetation on pulmonary valve leaflet.

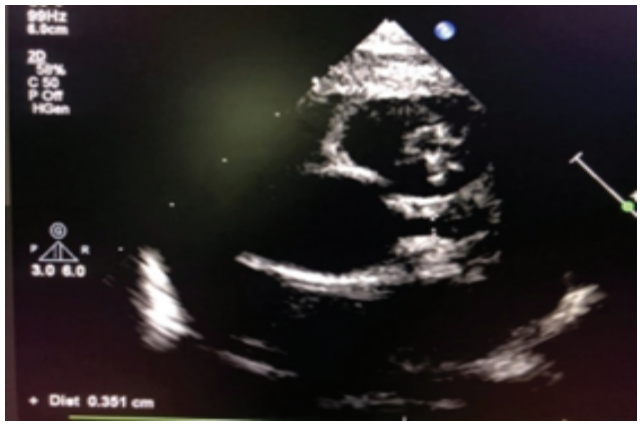

Fig 6 (case 2): Coronary artery aneurysm of left main coronary artery (LMCA) with vegetation on pulmonary valve.

The second child was previously diagnosed as infective endocarditis and was treated in other hospital for intravenous antibiotic for four weeks. However, in our hospital he was diagnosed clinically, by laboratory investigations and by echocardiography as MIS-C with infective endocarditis. He also had fever (103˚F), neutrophilic leukocytosis, thrombocytosis, high CRP, high D-dimer with left main coronary artery aneurysm and large vegetation obstructing pulmonary valve (Fig 5,6).Vegetation of first child was single, small, homogenous, almost globular, localized on the base of the pulmonary valve leaflets extending to tip. The shape, consistency and lack of stalk suggested that the vegetation might be caused by staphylococcal infection. The echogenicity of vegetation suggested that the lesion was caused by the microbial infection not more than two weeks[1]. The vegetation of the second child was large, diamond shaped, homogenous more echogenic which suggested formation of vegetation for prolonged time (Fig 5).

In addition, the child had congenital deformed pulmonary valve with stenosis over which the vegetation developed. The site of adherence of vegetation indicated that the traumatized valvular endothelium acted as nidus of microbial infection due to high velocity jet flow of blood through stenosed valve. Chest x-ray and slice CT suggested calcification of hilar lymph nodes. Blood culture reports revealed the growth of staphylococcus aureus in first case and staphylococcus saprophyticus in second case. The sequence of formation of vegetation leads to adhesion and entrapment of bacteria inside of NBTE and multiplication of microorganism increases the size. For the S. aureus these adhesions have been termed MSCRAMMs (microbial surface components recognizing adhesive matrix molecules[1].

Echocardiography is the confirmatory investigation to determine number, size, shape, location, echogenicity and mobility of vegetation. It is also useful for prediction of embolic risk. Both of the cases met Modified

Duke Criteria to be diagnosed as definitive case of infective endocarditis1. But we did cardiac multi slice CT (MSCT) in second case to determine accurate analysis of size, anatomy, calcification, abscess, infarction, any concomitant pulmonary vascular disease or embolism, even in distal pulmonary vasculature[4].

Sensitivity, specificity, diagnostic accuracy, and prognostic implications of the M-mode echocardiographic pattern of vegetation were examined prospectively in consecutive patients referred with potential active infective endocarditis (IE). It is useful to do 3D echocardiography for diagnosis of exact anatomy and location of vegetation which was done in first case. We did not need to do TEE (Trans esophageal echocardiography). It is reported that TEE is mandatory for evaluation of pacing or ICD leads vegetation[5].

In addition to infective endocarditis, both of the child developed MIS-C due to COVID-19, which was confirmed clinically, COVID antibody positive for the first case and by RT-PCR positive test for 2ndcase. RT-PCR positive indicated infection with COVID-19 within last two weeks whereas COVID antibody positive meant the patient had corona virus infection within last two to three months. Both of the lab results revealed recent contact or infection with COVID-19. However, for the first case, contact or infection by COVID-19 virus within few months could be the cause of inflammation of pulmonary valve, which acted as the nidus of vegetation. Repeated hospital admission and taking intravenous antibiotics by prolonged use of same intravenous line at hospital and even at home without proper hygiene maintenance could be the reason of bacterial infection results in infective endocarditis. We suspected the deformed valve is due to vegetation of infective endocarditis, as he had no murmur during his previous follow up with Pediatrician since birth. Nor withstand, he did not have any previous echocardiography report, which revealed his normal pulmonary valve.

Kumanayaka et al described a case study of infective endocarditis induced by COVID-19 infection. They described that COVID-19 was the cause of hyperactive inflammatory response along with hypercoagulable state leading to various complications[6]. Both of our children were admitted with recent history of fever. They were diagnosed clinically, by serological reports and echocardiography documents as MIS-C.

They had small aneurysmal dilation of all coronary arteries. The coronary architecture were almost smooth which revealed the inflammation were within two weeks[7].Coronary artery internal diameter were taken and plotted in z-score (Boston criteria) and classified as AHA guideline of Kawasaki disease[8].
Different blood samples sent on different time from different sites showed staphylococcus aureus and staphylococcus saprophyticus in blood culture. For the first patient according to culture sensitivity test we could complete intravenous ceftriaxone and vancomycin for 6 weeks. Meanwhile, we saw the clinical improvement of the child. Echo revealed the gradual reduction and disappearance of vegetation. However, the damage of the pulmonary valve was permanent which caused free pulmonary regurgitation.

Nevertheless, for the second patient there was surgical indication for removal of vegetation because of the big size (>10mm) (Fig 5), pulmonary valvular obstruction and also nonresponsive to medical therapy even after 4 weeks. As the child was diagnosed clinically as MIS-C with fever more than 3 days, neck rigidity and respiratory distress coronary aneurysm with evidence of coagulopathy and elevated markers of inflammation (raised CRP) the child was treated with IVIG, intravenous methylprednisolone. But tab aspirin was not given. Because anticoagulation (aspirin) is controversial during treatment of native valve infective endocarditis due to increased risk of cerebral hemorrhage because of association with cerebral septic embolism[9].
Their fever subsided within 24 hours of IVIG infusion. Coronary artery aneurysms were normal in caliber within seven days. Both of these children were on follow up according to CDC and WHO protocol[10,11].
The second patient needed surgical removal of vegetation after completion of intravenous antibiotic for six weeks. As there was no change of shape, homogeneity or reduction of size of vegetation. Perioperative biopsy of vegetation revealed mycobacteria tuberculosis.
The first child with flail pulmonary valve with severe pulmonary regurgitation is on follow up with medical management. He has no clinical or echocardiographic evidence of right heart impairment. The second patient is fully cured after surgery and completion of anti TB medicine and intravenous antibiotics for six weeks.

CONCLUSION

COVID-19 virus causing MIS-C were common scenario during 2020 to 2021 in Evercare Hospital Dhaka. But prevalence of infective endocarditis due to COVID -19 or IE with association with this notorious virus were rare. Clinical evidence and laboratory diagnostic tools along with expert echocardiography lead the treatment process for IE on perfect way.

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