CASE REPORT

Infantile intracardiac thrombus in severe encephalo-myocarditis

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SUMMARY

Myocarditis is an uncommon disease in childhood and has a wide range of clinical presentations, from subtle to devastating and thus requires a high index of suspicion. Intracardiac thrombus formation following myocarditis is rare and thus its management remains challenging and not well defined. We report a child whom presented with a viral prodrome, rapidly deteriorated into multi organ failure and developed fulminant viral myocarditis with encephalitis that was complicated with an intracardiac thrombus formation. We describe the challenges faced, the successful medical treatment offered and propose factors that can help guide appropriate treatment.

INTRODUCTION

Myocarditis is an uncommon disease in childhood that often follows cardiotropic viral infections and can lead to significant morbidity including cardiac failure, thrombosis, arrhythmias, dilated cardiomyopathy, and sudden death. Intracardiac thrombus formation following myocarditis is rare and its management remains challenging and not well defined. We report a case of successful medical treatment of a 3-month-old previously well female infant with fulminant viral myocarditis and encephalitis that was complicated with an intracardiac thrombus formation and highlight the factors that can help guide appropriate treatment.

CASE REPORT

A 3-month-old previously well female infant was admitted to a peripheral hospital for high grade fever, recurrent vomiting, and papulovesicular rashes over the wrists and knees for three days. She was mildly dehydrated and there were no abnormal physical signs. Initial laboratory investigations revealed C-reactive protein 198.2g/dL, hemoglobin 10.9g/dL, white cell count 17.25 x 10^9/L (neutrophil 53%, lymphocyte 38%, monocytes 8%, eosinophil 1%), platelet count 783 x 10^9/L and transaminitis (aspartate aminotransferase 126 U/L, alanine transaminase 108U/L). She was treated for a presumed bacterial infection with intravenous (IV) ceftriaxone and IV hydration. On the third day, she experienced sudden clinical deterioration with increasing tachypnoea (58/min), tachycardia (170/min) and a brief seizure that aborted spontaneously. Following IV fluids resuscitation, her tachypnea and tachycardia worsened, she was electively ventilated and was transferred to our center for continued care.

Her ventilation was optimized on arrival. Blood pressure 90/45mmHg. Cardiovascular examination found shifted apex beat, tachycardia with gallop rhythm, and hepatomegaly 2.5cm from the right costal margin. Neurologically, she had sluggish pupil reactivity, hypertonia, and persistent thumb adduction with fisting. Faint healing papulovesicular rash visualised over knees and wrists bilaterally. Laboratory investigations revealed elevated biomarkers (troponin T 164.2ng/L, creatine phosphokinase 696U/L, creatine kinase-MB 9.4ng/mL, aspartate aminotransferase 2735U/L, alanine transaminase ALT 934, lactate dehydrogenase 3452U/L, ferritin 541.6ng/ml). Chest radiograph displayed bilateral interstitial opacities with mild cardiomegaly, consistent with pulmonary edema. Electrocardiography showed sinus tachycardia with right ventricular hypertrophy (Figure 1). Our preliminary diagnosis was fulminant viral myocarditis, pulmonary edema, and encephalitis.

The first echocardiogram demonstrated dilatation of left heart chambers, poor left ventricular function with left ventricular ejection fraction (LVEF) of 31%. There was mild to moderate mitral and tricuspid regurgitation with no evidence of ventricular non-compaction. No pericardial effusion or intracardiac thrombus was visible.

Cerebrospinal fluid and stool for polymerase chain reaction (PCR) and culture were negative for cardio-neurotropic viruses.

Electroencephalography showed diffusely attenuated background with lack of variability and consisted of low amplitude delta activity (up to 75uV) intermixed with theta activity and bilateral sleep spindles. Magnetic resonance imaging (MRI) brain showed multiple tiny punctate foci that was hypointense on T1 weighted imaging, hyperintense on T2 weighted imaging and restriction diffusion on ADC and DWI sequence, over the thalamus and cerebellum bilaterally (Figure 2). These changes are in keeping with an acute arterial ischemic insult.

Treatment initiated included IV acyclovir and IV ceftriaxone, and for congestive heart failure IV milrinone infusion, low dose IV dopamine and IV furosemide. Intravenous immunoglobulin (IVIG) (2g/kg) infusion was started as adjunctive treatment for viral associated encephalitis and myocarditis.

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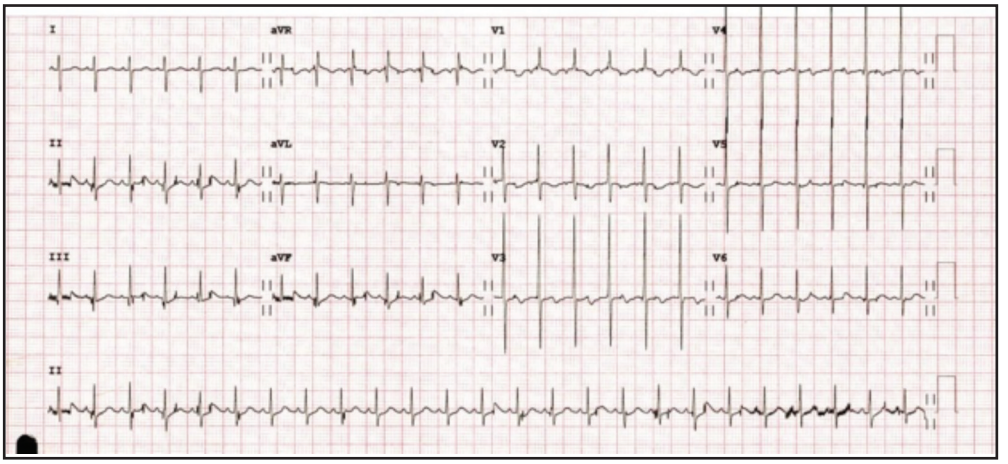

Fig. 1: Electrocardiography showing sinus tachycardia (heart rate 152/min) with right ventricular hypertrophy.

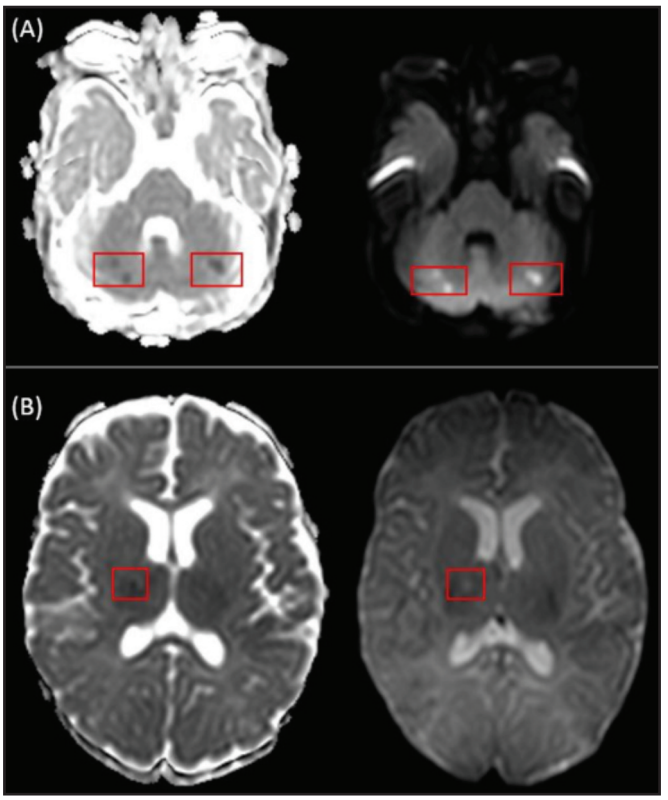

Fig. 2: MRI brain (Apparent diffusion coefficient/Diffusion weighted imaging sequence) showing restricted diffusion (red box) over bilateral cerebellar white matter (A) and right thalamus (B).

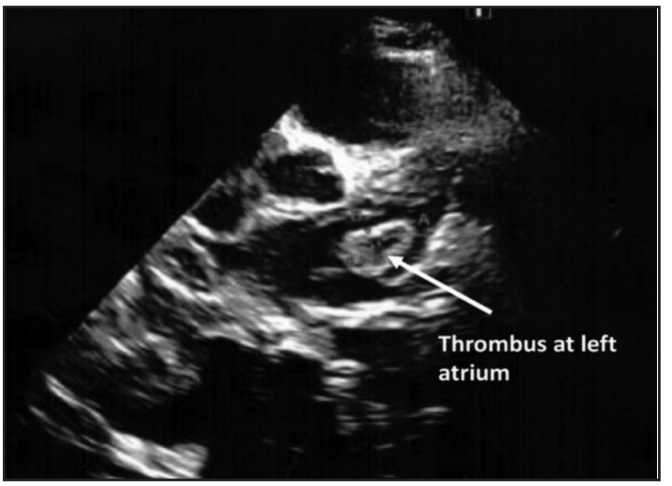

Fig. 3: Echocardiography on day 6 admission showed a large left atrial thrombus at the left atrial appendage and extending to the body of the left atrium, measuring 8mm x 11.4mm.

LA: left atrium, RA: right atrium, LV: left ventricle, RV: right ventricle, Ao: aorta

Video 1: https://drive.google.com/file/d/1h2Z1x4L3y8WRDx37LX6r67Lh5Heh-Vqu/view?usp=sharing

The patient was ventilated for eight days, then weaned to continuous positive airway pressure, and finally nasal oxygen that was discontinued at day 15 of admission.

Echocardiogram on day-6 of admission detected a large left atrial thrombus at the left atrial appendage and extending to the body of the left atrium, measuring 8mm x 11.4mm. It was pedunculated and non-mobile. Left ventricular function was impaired with LVEF of 44% (Figure 3 Video 1). Hematological investigations did not reveal hypercoagulopathy. The was no cardiac arrhythmia. The stasis of blood within the poorly functioning myocardium had likely resulted in the thrombus formation.

Surgical thrombectomy was initially considered given the risk of thromboembolism. However, as our patient remained critically ill with severe neurological insult and impaired cardiac function, a trial of medical treatment was jointly agreed upon. IV heparin infusion was commenced for the first two weeks followed by subcutaneous low molecular

weight (LMW) heparin. There was a consistent reduction in the size of the intracardiac thrombus over four weeks with improved cardiac function (LVEF of 62-70%). Complete resolution of the intracardiac thrombus was achieved at day 43 post-admission with no occurrence of thromboembolic events.

She made a gradual neurological recovery with no seizures witnessed throughout admission. She developed transient cerebral salt wasting requiring sodium chloride supplementation for 1 month. The long-term neurological prognosis remains guarded.

DISCUSSION

Myocarditis is defined as an inflammatory disease of the heart muscle diagnosed by established histological, immunologic, and immunohistological criteria. Patients of all ages may be affected, but the majority of cases occur in infants and teenagers; particularly in the first year of life.

In a Finnish national registry study of children, the incidence of myocarditis was approximately 2 in 100,000 patient-years.[1] There are nearly 20 known cardiotropic viruses that have been implicated as a cause for myocarditis, of which enteroviruses, particularly coxsackie group B serotypes, are the commonest. More recently, viral genomes from endomyocardial biopsies have shown parvovirus B19, human herpesvirus 6, and adenovirus to be increasingly common.[1]

The cardiotropic virus in myocarditis can be identified by viral PCR of endomyocardial biopsy, respiratory tract, blood, urine or stool samples. The absence of a positive PCR, however, does not exclude a viral cause as the viremic phase may have resolved before cardiac manifestations.

Clinical presentations of paediatric myocarditis can vary from subtle findings of tachypnoea and tachycardia to fulminant myocarditis and cardiogenic shock, within days to weeks of a viral infection. It is not unusual for the fulminant form to be mistaken for sepsis or severe dehydration in children, and commencement of large volumes of resuscitation fluids can lead to pulmonary oedema and cardiovascular collapse, as in our case. A high index of suspicion is necessary for early diagnosis as clinical judgment, with supporting ancillary tests, remains the mainstay of diagnosis.

The general approach for myocarditis is supportive. Some centres advocate the early use of intravenous immunoglobulin (IVIG) in children due to its antiviral and anti-inflammatory effects. One paediatric trial from the Cochrane Collaboration Review of 2015 (Bhatt 2012) suggested that benefits may be seen in children with acute encephalitis syndrome complicated by myocarditis.[2]

Treatment of congestive cardiac failure include diuretics, afterload reduction, inotropic support, anticoagulation, arrhythmia management, and ventilatory support. Low dose dopamine (≤5µg/kg/min), dobutamine and low-dose epinephrine (≤0.05µg/kg/min) help increase contractility via their actions on myocardial beta-adrenergic receptors while minimizing associated vasoconstriction. Milrinone has positive inotropic and vasodilatory effects without increasing myocardial oxygen consumption. Those with more severe cases of myocarditis may require circulatory support in the form of extracorporeal membrane oxygenation or ventricular assist devices.[1]

The risk of thrombotic events in children with myocarditis is currently unknown, leading to uncertainty regarding the need for antithrombotic therapy. A retrospective study of 28 paediatric patients with myocarditis reported that 11.1% experienced intracardiac thrombosis.[3]

Several factors place children with myocarditis at increased risk of thrombus formation, including stasis of blood in a poorly functioning heart, and inflammation of the myocardium and surrounding structures. Some studies in children with dilated cardiomyopathy suggest that those with severely diminished or rapidly deteriorating ventricular function are at highest risk of thrombus formation.[3] The biggest concern of intracardiac thrombus is its risk of peripheral embolization particularly to the brain and kidneys leading to high mortality with a reported embolisation risk of 13%.[4]

The treatment approaches for paediatric intracardiac thrombus described include thrombolytics (tissue plasminogen activator (t-PA), streptokinase, urokinase) and/or anticoagulants (classical/LMW heparin, warfarin) or surgical thrombectomy.[5] The traditional therapy for intracardiac thrombi in paediatric patients has been surgical thrombectomy, but there are increasing reports of successful non-surgical strategies.[4]

Patients with thrombus causing important hemodynamic abnormalities (obstruction to flow with symptoms or signs, interference with valve function) or at high risk of embolisation (poorly adherent or mobile thrombus, thrombus located in an area of high flow) should receive thrombolytic therapy or surgical thrombectomy.

Balancing the risk of surgical thrombectomy versus medical therapy is difficult. With anticoagulation therapy, a pedunculated thrombus risks becoming more unstable due to additional narrowing of the thrombus stalk and thus promoting embolism.

Conversely, the presence of underlying myocarditis with poor left ventricular function would lead to additional deterioration of myocardial function following cardiopulmonary bypass and cardioplegic arrest. Furthermore, patients with pre-operative neurological insult are vulnerable to cardiopulmonary bypass related neurologic injury. In view of this, we felt intravenous heparin infusion was the appropriate initial first line treatment option. Further, we decided against the use of thrombolytic therapy as this was an acute thrombus, and it has shown to be associated with higher mortality due to major bleeding in young infants.[5]

We recognise that the multiple punctate lesions with restricted diffusion seen in the MRI brain, may represent infarct of end arteries. Considering the clinical scenario, multiple factors could account for this, however embolic infarct would be the most likely pathology.

Intravenous (IV) heparin has been shown to be highly effective and safe for thrombi with high-risk features for embolization then once stable switch to low molecular weight (LMW) heparin.

The early use of IV immunoglobulins, inotropic and vasodilatory therapy, and aggressive anticoagulation therapy had likely contributed to the complete resolution of the intracardiac thrombus and normalization of left ventricular function.

Despite extensive investigations, we were unable to identify the causal organism. The distributive pattern of papulovesicular rashes over her limbs prior to the onset of neurological, and cardiovascular compromise though nonspecific, suggests the possibility of enterovirus infection. The rash in toxic shock syndrome due to Staphylococcal and Streptococcal infections usually present with mucosal and conjunctival hyperaemia, diffuse erythroderma, necrotizing fasciitis and desquamation of palms and soles, none of which was present in our case.

CONCLUSION

Intracardiac thrombus formation following fulminant myocarditis in children is rare but has potentially fatal consequences. Treatment decisions of such cases with medical anticoagulation or surgical thrombectomy should be guided on a case-to-case basis by the patient's hemodynamic status, cardiac function, and thrombus characteristics. The role of prophylactic anticoagulation therapy in children with myocarditis remains unclear and should be a focus of future research.

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