

Treatment with intravenous immunoglobulin in a subclinical neonatal myocarditis – Review of the literature and a case report

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ABSTRACT

Myocarditis is an inflammatory disease of the myocardium that is associated with significant morbidity and mortality. We present the case of a male infant born at 38 weeks gestational age detected with subclinical myocarditis. The diagnosis was suggested by the raised cardiac enzymes, small voltages on electrocardiogram and biventricular hypertrophy on echocardiography. The newborn was managed with supportive, immunomodulatory therapy, diuretics and anti-platelet agents (Aspirin). Early intravenous immunoglobulin administration may have helped to reduce morbidity and mortality, even if administration of intravenous immunoglobulin is not yet clearly established in the neonatal population.

Keywords: myocarditis, newborn, cardiac enzymes, intravenous immunoglobulin

INTRODUCTION

Myocarditis is an inflammatory disease of the myocardium that is associated with significant morbidity and mortality [1]. The inflammation is presumed to most commonly start as an infectious process, although autoimmune and idiopathic forms also occur [2]. Myocarditis diagnosed amongst pediatric population are based on viral DNA-emia detected by blood polymerase chain reaction, non-specific clinical symptoms, abnormal echocardiography, electrocardiogram (ECG) and elevated cardiac specific enzymes, but it may exist also

in neonatal period in the absence of all of these abnormalities [1,3-5]. There is substantial variation in patient presentation ranging from subclinical or non-specific symptoms to acute heart failure or even sudden cardiac death [1].

Signs of myocarditis are non-specific and include respiratory distress, tachycardia, cardiomegaly, arrhythmias and ECG sign of myocardial injury, then cyanosis and circulatory collapse develop rapidly [6]. Even patients with mild symptoms are at risk of deterioration, and therefore early diagnosis is important in establishing appropriate monitoring and supportive care [7].

The chest x-ray classically displays cardiomegaly and pulmonary venous congestion [8]. ECG changes in neonatal myocarditis are variable and include ST-segment elevation or depression, T wave inversion or flattening, prolonged QTc, QRS widening, abnormalities in atrio-ventricular conduction and bradycardia or atrial or ventricular arrhythmias (supraventricular or ventricular ectopic beats) are frequent findings [9]. Laboratory tests suggestive of myocarditis generally include elevation of troponin and BNP levels [10]. Myocyte necrosis in myocarditis can be evaluated by measuring serum Troponin level which was usually elevated earlier than creatine kinase muscle brain (CK-MB) in acute myocarditis [11]. Measuring C-reactive protein (CRP) that is a nonspecific serum marker for systemic inflammation and also, elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) for the assessment of heart failure may be helpful [11]. The echocardiography is essential in the diagnosis and follow-up of myocarditis [8].

The diagnosis of myocarditis among older infants is suggested by ischemic signs on ECG, raised specific cardiac enzymes, and left ventricular (LV) dysfunction on echocardiography [9]. Dilated cardiomyopathy is a common and severe complication of myocarditis [12]. Intravenous immunoglobulin (IVIg) is a serum product made up of Igs, gathered from the blood of more than a thousand donors per batch [11]. IVIg is used at two different doses including a low dose (200 to 400 mg/kg, three times a week) and a high-dose (2 g/kg, monthly) [11]. IVIg therapy should be started as early as possible before severe necrosis of the myocytes has occurred [9].

High-dose IVIg has shown potential in the treatment of myocarditis, hypothetically due to its antiviral, antibacterial, and immunosuppressant properties [13]. High-dose administration of IVIg is connected with improved LV ejection fraction (LVEF) recovery and with a more remarkable survival rate during the first year [11].

The aim of this article is to present a newborn with soft dysmorphic features detected soon after birth with a cardiac murmur and elevated cardiac enzymes in order to show a rare neonatal condition that should be considered in the differential diagnosis of congenital disorders or genetic syndromes. Written informed consent was obtained from the patient's mother, the minor's legal guardian, for the publication of this case report.

CASE REPORT

Presenting concerns

We present the case of a male infant born at 38 weeks gestational age (GA). His 33-year-old mother was a G3P3; the pregnancy was uncomplicated. She does have not any significant medical history and takes no

medication. The birth was vaginal and fetus was in cephalic presentation. The amniotic membranes ruptured 20 minutes before birth and the amniotic fluid was greenish. The infant's birth weight was 3300 g (49th centile), length 51 cm (48th centile) and cranial perimeter 34 cm (26th centile). His Apgar scores were 7 and 8 at 1 and 5 minutes. He had a delayed cry and needed upper respiratory air ways suction, gentle tactile stimulation, positive pressure ventilation on the mask with T-piece resuscitator (peak inspiratory pressure/positive end-expiratory pressure: 25/5 cmH₂O, fraction of inspired oxygen: 25%) for 1 minute and then free flow oxygen for 30 seconds. The early postpartum adaptation was good except generalized hypotonia. He was transferred to neonatal intensive care unit and was started on supportive care and continuous monitoring of vital functions.

Clinical findings

On examination the newborn was alert and appeared well. The temperature was 36.5°C. There were few dysmorphic features such as small and low set ears, hypertelorism, wide base for nasal implantation, marked integumentary excess at the level of the neck, small and square hands. The reflexes were diminished with mild generalized hypotonia. The anterior fontanelle was flat and soft. On physical exam, the lungs were clear on auscultation. The respiratory rate was 50 breaths/minute, without signs of respiratory distress and the oxygen saturation while he was breathing ambient air was 96-100% without pre- and postductal differences. The heart sounds were rhythmic, heart rate 143 beats/minute, with a systolic murmur grade II/6 left parasternal and the blood pressure of 65/36 (47) mmHg preductal and 62/47 (51) mmHg postductal. The remainder of the physical examination was normal.

Diagnostic focus and assessment

The CRP and procalcitonin values were in normal range and blood cultures were negative during hospitalization. The initial levels of lactate dehydrogenase (LDH), CK and CK-MB was 1449 units/liter (U/L), 72 U/L, 39 U/L; in the next days of life these enzymes levels dropped to normal limits by the second week of life. The cardiac enzymes were gradually increased from day 3 to day 7 of life. The highest level of troponin was 66.4 pg/ml, of NT-proBNP 1847.3 pg/ml and of D-dimer 35.2 mg/L.

For differential diagnosis of the Pompe disease the level of alpha-1.4 glucosidase activity was determined and it was in normal range (alpha-1,4 Glucosidase lysosomal enzyme activity was 8.2 micromole/L/h, the cut-off value higher than 2). The presence of viral DNA detected by polymerase chain reaction (PCR) for enterovirus, adenovirus and human herpesvirus were nega-

tive. No additional tests for the presence of other cardiotropic viruses were performed due to not availability of such tests at the time when infant was hospitalized.

A chest x-ray revealed that the lungs were clear, with no pleural effusion. The heart size was abnormal with a cardiothoracic ratio greater than 50%, suggestive for cardiomegaly. A cranial and abdominal ultrasound was completed at 24 hours of life and they were unremarkable.

The infant had three echocardiography assessments in the first 2 weeks of life. Initial echocardiogram performed at 48 hours of life was notable for low velocity bidirectional patent ductus arteriosus (PDA) shunt, bidirectional shunt across the foramen ovale (PFO), right ventricular (RV) hypertrophy without RV dysfunction (TAPSE 1.1 cm) moderate LV hypertrophy with mild LV systolic dysfunction (EF by Simpson 48%) with markers of LV dysfunction (E/A 0.7) and mitral valve regurgitation (MV max 1.75 m/sec, PG max 1.75 mmHg). The echocardiography revealed also elevated pulmonary pressures based on the position of interventricular flat septum in systole and diastole, and no concern for LV outflow obstruction. (See figures 1-7 recorded at day 2 of life). Repeated echo on day 7 of life noted normal cardiac structure, improvement of LV function, no flow detected at PDA level and the presence of left to right shunt at the interatrial septum. His echo at the time of discharge was notable for normal RV size and function, LV hypertrophy and normal systolic function (EF by Simpson 54%), no mitral regurgitation detected, dropped pulmonary pressure based on round interventricular septum and a small left to right shunt at the PFO level.

The ECG was performed to detect any atrioventricular conduction abnormalities. The initial ECG was in sinus rhythm, QRS axis deviated to the extreme right and without rhythm or cardiac conduction disorder. In evolution the ECG became low voltage with more flattened T waves. Then a Holter ECG monitoring showed sinus rhythm with a maximum heart rate of 186 beats/minute – sinus tachycardia, atrial extrasystoles with aberrant conduction, isolated or bigeminal (arrhythmic load <1%), monomorphic ventricular extrasystoles, isolated (arrhythmic load <1%), without supraventricular and ventricular tachyarrhythmias. The Holter ECG monitoring showed supraventricular and ventricular extrasystolic dysrhythmia.

Both laboratory and imaging techniques are essential diagnostic tools for myocarditis. At nine days of life our case was interpreted as an acute myocarditis and the diagnosis was sustained by the elevated cardiac enzymes, abnormal low voltage on ECG, supraventricular and ventricular extrasystoles, cardiomegaly seen in the

initial chest roentgen and serial echocardiographic findings of biventricular hypertrophy.

Therapeutic focus and assessment

When the diagnosis of acute myocarditis was made, treatment recommendation at this point was beside supportive therapy, immunomodulatory therapy with IVIG in a single dose of 2 g/kg/24 hours, diuretics and anti-platelet agents (Aspirin). Improvement in cardiac function was described by echocardiography after use of IVIG in our case and no adverse event was observed with IVIG administration.

Follow-up and monitoring

A multidisciplinary bedside approach with neonatology, pediatric cardiology and medical geneticist was performed in a setting of a newborn with stable clinical state without sign of hemodynamic instability and based only on non-specific laboratory tests, mild ECG and echocardiographic findings to manage the unclear underlying pathology. The newborn was discharged from the maternity unit at the fifteenth day of life. He remained stable, with an upward growth curve and with blood tests with normal values. The case was discharged at home, with close supervision by the pediatric cardiology.

DISCUSSIONS

Myocarditis is an uncommon disease in neonates [14]. Similar to our case, Lee et al revealed that the ECG examination described abnormal rhythms in 58.8% in a small study of 17 cases detected with myocarditis. Also, cardiomegaly (cardiothoracic ratio >0.5) was detected on chest x-ray in all patients included in his study [15].

The male neonate's case of myocarditis and meningitis described by Li et al had a level of LDH of 1102 U/L and higher levels of BNP, CK, troponin-I and CK-MB, probably because of the association with meningitis [16]. Increased cardiac enzymes are indicative for myocardial damage, but occur in myocardial infarction as well as in myocarditis; follow-up echocardiography will show more global abnormalities in myocarditis [12].

Like in our case, Lee et al revealed that all 17 patients received IVIG 2 g/kg as soon as the diagnosis of myocarditis was considered [15]. However, Robinson et al showed that IVIG administered for 86 children favoured but did not significantly improve survival [17].

The timing of IVIG administration is crucial and early IVIG may be beneficial for survival in severe cases [6]. In contrast to our case, the male neonate described by Roy et al received IVIG at 1 g/kg/day for two days [18]. Schauer et al have used high dose of steroids in association with IVIG to treat myocarditis [1]. Regarding of

treatment for myocarditis, Li et al stated that IVIG might be beneficial to improve LVEF and survival, but the present evidence does not support corticosteroids as superior to conventional therapy [19].

IVIG has become part of routine immunomodulatory therapy for treating children with acute myocarditis at many centres, in a standard high-dose of 2 g/kg/24 hours [20]. However, more targeted therapy based on recent research are warranted as IVIG use amongst neonates carries the potential risk of necrotizing enterocolitis [21].

CONCLUSIONS

Myocarditis is a rare but potentially life-threatening disease in neonatal period and the risk is that often to

death or important morbidity among survivors. Manifestations of myocarditis were present soon after birth in this case of negative PCR subclinical myocarditis and the outcome was improved with care and treatment. Early IVIG administration may have helped to reduce morbidity and mortality, even if administration of IVIG in neonatal myocarditis is not considered as a standard care yet. Because myocarditis is a serious condition, more researches are needed to help physicians be aware of infants at risk for adverse outcome and to specify which neonate need the immunomodulatory therapy.

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