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Paediatric Restrictive Cardiomyopathy - Diagnosis and Challenges

A report of two cases

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Abstract:
Restrictive cardiomyopathy is one of the rarest forms of cardiomyopathies in pediatric patients characterized by impaired myocardial relaxation or compliance with restricted ventricular filling, leading to a reduced diastolic volume with a preserved systolic function. We report two cases – a 5-year-old boy who presented with abdominal distension and palpitation with family history of similar complaints but no definite genetic diagnosis as yet, and a 5-year-old girl who presented with chronic cough and shortness of breath. Both cases were diagnosed in Sultan Qaboos University Hospital in 2019 and are managed supportively with regular outpatient follow-up. This is the first series of reported cases of pediatric restrictive cardiomyopathy from Oman.

Keywords: restrictive cardiomyopathy, cardiomyopathy in children, heart failure in children

Introduction

Restrictive cardiomyopathy (RCM) is one of the rarest forms of cardiomyopathies in pediatric patients, with an overall prevalence of 2-5% of all types of cardiomyopathies.[1] Functionally, RCM is characterized by impaired myocardial relaxation or compliance with restrictive filling, leading to a reduced diastolic volume with a preserved systolic function.[2] This leads to atrial dilatation, which is represented by the large P-waves on an

electrocardiogram (ECG) and bundle branch block.[1] Findings in an echocardiogram illustrate atrial dilatation and small ventricles, with an element of atrioventricular regurgitation that worsens the atrial enlargement.[1] The causes of RCM are divided into primary and secondary , and subdivided into familial/sporadic causes and systemic disorders, respectively.[3] Secondary causes are usually seen in adults and include systemic infiltrative diseases like amyloidosis, Gaucher's disease, and storage disorders like Fabry's disease and others including scleroderma, endomyocardial fibrosis, and carcinoid syndrome.[3] RCM can be confused with constrictive pericarditis and is challenging to differentiate clinically and with imaging; however, it is important to differentiate them as the latter can be treated surgically, whereas the former has a high mortality rate.[1] The reported complications of RCM include heart failure and arrhythmias compared to the rarer complications including thromboembolism, and increase pulmonary vascular resistance.[4]

We report two patients with restrictive cardiomyopathy both presenting at an early age of 5 years – one male with abdominal distension and palpitation, and one female with chronic cough and shortness of breath.

Case reports

Case 1

A 5-year-old previously healthy boy presented with history of gradually worsening abdominal distension of ten-days duration. It was associated with palpitations. He had a history of recurrent fever and upper respiratory tract infections (URTI) requiring intravenous antibiotics in a private clinic for two days. The mother also gave history of decreased appetite with poor weight gain over the past 4 months. Rest of the history was unremarkable.

He is the fourth child born to first degree consanguineous parents with five other siblings. Two of his brothers had expired with a similar presentation. His oldest brother passed away at the age of 24 years after being admitted with abdominal distension, the details of which are not available. He was suspected to have a restrictive cardiomyopathy. The older brother had other medical problems including atrial flutter, hypothyroidism, liver cirrhosis, and hypogonadism and had also received testosterone briefly. The second brother who expired also had developed abdominal distension at the age of 5 years and passed away at 12 years of age with no definite diagnosis. No other family history of cardiac diseases or sudden deaths in the family.

On assessment, this child looked active, pale, with no dysmorphic features. His weight was 15 kg (<10th centile) and height 106 cm (25th centile). He was stable on admission and cardiac examination revealed a normal S1 and loud S2. The chest was clear with bilateral normal breath sounds. Abdomen was distended on inspection with visible abdominal veins. There was a non-tender hepatomegaly of 7 cm below the right costal margin and no splenomegaly. Rest of examination was normal. As a result, he was first worked up by the gastroenterology team and was referred to cardiology once gastro-intestinal causes were ruled out.

Laboratory findings are illustrated in table 1. Abdominal ultrasound revealed enlarged echogenic coarse liver suggestive of liver parenchymal disease and congestive hepatomegaly. Hepatic veins and intrahepatic inferior vena cava were dilated. Chest x-ray was done on admission and was unremarkable.

ECG findings are shown in table 2. The echocardiography showed severely dilated right and left atrium with severe tricuspid valve regurgitation along with a trivial mitral regurgitation. It also illustrated mildly reduced systolic function with ejection fraction of 50% and the left ventricle showed apical trabeculations with features suggestive of non-compaction. There was no pericardial effusion. The detailed findings of the echocardiography are shown in table 3 and figure 1. The 24-hour Holter electrocardiogram was normal.

He was started on furosemide, spironolactone, and digoxin. Currently, he is followed with cardiology every 6-8 months and has had two admissions since diagnosis for chest infections. Consent has been obtained from patient's guardian.

Case 2

This is a 5-year-old previously healthy girl, who presented with a 4-day history of cough and poor oral intake. There was no history of fever, no shortness of breath and no exposure to sick contacts. She had a history of night sweats and palpitations that were aggravated by change of posture. There was no history of chest pain, cyanosis, or syncope. She had a similar episode 1 month prior and was treated symptomatically elsewhere. Father gave history of easy fatigability with running as compared to his other children and also poor appetite and poor weight gain for the past two years. There is history of inability to sleep

lying flat and needing head elevation for the last few months. She had cataract surgery at the age of 3 years.

She is the eldest child of first degree consanguineous parents. One of her paternal cousins had a cardiac defect that needed catheterization, but no details were available. She also had a maternal aunt who developed valvular heart disease at the age of 12 years and required valve replacement. She has 3 other younger siblings who are doing well. There is no history of other cardiac disease in the family.

On physical assessment, child was in respiratory distress with mild recessions and tachypnea up to 30 breaths per minute. Her weight 14.75 kg (10^{th} centile), and height 114.5 cm (10^{th} centile). She had periorbital edema with hypertelorism and clubbing. Chest examination revealed bilateral basal scattered crepitations. Cardiac examination revealed normal heart sounds, with gallop and a pansystolic murmur grade II/VI best heard at the apex. Abdominal examination revealed distension and tender hepatomegaly of 8-9 cm below the right costal margin.

Laboratory findings are depicted in table 1. Chest x-ray showed cardiomegaly with congested lungs and right para-cardiac haziness. Electrocardiogram findings, and echocardiography findings and diagram are shown in table 2, table 3, and figure 1, respectively. Her initial working diagnosis was Multisystem Inflammatory Syndrome in children (MISC) causing acute heart failure. She also had a full septic work-up to rule out pneumonia, pleural effusion, and myocarditis, and was initially started on furosemide and spironolactone. During her further admissions digoxin, captopril, and aspirin were added gradually. The genetic and metabolic teams were involved to exclude secondary causes. At the last follow up, she was intermittently in atrial flutter-fibrillation needing higher doses of digoxin for rate control. Consent has been obtained from patient's guardian.

Discussion

Restrictive cardiomyopathy (RCM) is one of the common causes of adult diastolic heart failure, which could be explained by the different risk factors affecting this age group.[5] In contrast, these risk factors are absent in the pediatric age group, making this type of cardiomyopathy a rare occurrence in children with incidence of 0.04/100,000 in the United

states.[6] It is mostly diagnosed between the ages of 6-10 years, corresponding to our cases, where both patients were 5 years of age.[5] Both cases in our series were idiopathic.

As per the American Heart Association (AHA), the most common mode of inheritance is autosomal dominant.[7] Our first case, the 5-year-old boy also had a strong family history of cardiac diseases and sudden deaths suggesting autosomal dominant inheritance, though no genetic diagnosis was confirmed till this report.

RCM presents with a wide variety of symptoms, making the diagnosis even more difficult. In different case studies, a 10-year-old boy collapsed as he was playing football and was found to have a large liver and high B-type natriuretic peptide (BNP), along with abnormal echocardiography findings, consistent with RCM.[5] Again, both our patients also presented with hepatomegaly, along with cough and fever. The other patient in Dienfield's study also had recurrent respiratory illnesses, similar to our cases. These presentations are mostly due to the high filling pressures that cause pulmonary edema, pulmonary hypertension, hepatomegaly, and peripheral edema.[5] On the other hand, a case reported from Saudi Arabia where an 11-year-old girl presented with lower limb swelling and paresthesia with no chest pain or shortness of breath, diagnosed with thromboembolism and RCM and treated with cardiac transplant.[8]Therefore, the non-specific signs and symptoms of RCM may lead to an initial diagnosis of different respiratory or alimentary illnesses, and the cardiac diagnosis may be missed or delayed as in our two cases reports.

Our first case was admitted under general pediatrics and the initial assessment was done by the gastroenterology team. Once the gastroenterology causes were ruled out, he was referred to the cardiology team. The main cause of delay in the diagnosis was the presentation with abdominal distension with hepatomegaly hence causes like liver diseases and malignancies were ruled out before looking for other causes.

Our second case had chronic nonspecific cough for the last 2-3 months. She was seen elsewhere by general pediatrician and was treated as acute chest infection vs asthma. The chest x-ray done outside showed borderline cardiomegaly which was missed as were the important details in history like worsening inability to lie flat and easy fatigability.

Both cases presented with non-cardiac symptoms which led to a delay in the diagnosis. These cases underscore the importance of a good history and physical examination and the need to approach patients with chronic complaints with a wider frame of mind.

The diagnosis of RCM can be done by utilizing the electrocardiogram, echocardiography and cardiac MRI if needed. The main finding as per the AHA, is the biatrial enlargement on echocardiography and surface ECG with preserved systolic function.[7]

Commenting on the diastolic function in the pediatric age group may be difficult due to the variability of presentation or the need for sedation.[8] Echocardiography can also differentiate between RCM and constrictive pericarditis (CP), which changes the management completely.[9] In CP, the chamber compliance is reduced due to external pressure, causing an increased interventricular dependence and irregularity between intracardiac and intrathoracic pressure during respiration as shown by doppler echocardiography along with septal shifting.[10] More specifically, annular tissue doppler can further distinguish the two entities. In RCM, the early diastolic velocity of mitral annulus (e') is reduced, whereas it is normal or increased in CP.[10] Cardiac catheterization shows similar features in both diseases including early rapid diastolic filling with elevated end-diastolic pressures.[10] The main finding to differentiate CP from RCM is the respiratory variation in pressures.[10] Biopsy of the endocardium in children with RCM is not specific and is not helpful in making the diagnosis.[9]

The prognosis of RCM is generally poor, with a survival rate of about 2 years from the day of diagnosis.[11] Management of RCM is mainly symptomatic, involving diuretics in pulmonary congestion, pacemakers in arrhythmia, and anticoagulants in a thromboembolic event.[12] The use of diuretics should be carefully assessed as they are preload dependent and we should not dry them.[12] There is no proven role for Digoxin and beta-blocker however, it might be helpful with tachyarrhythmia or heart rate control.[5,13] The definite therapy is a cardiac transplant which showed the 10-year survival rate post-transplant to be similar to other types of cardiomyopathies.[12] The outcome of transplant has improved with a median graft half-life of 12 years.[11] The question of when to send such cases for heart transplantation is still controversial; however since medical therapy is just symptomatic many centers post these cases for transplant immediately after diagnosis.[11] The final decision lies with the institute itself and their own criteria.[13] A case series from Spain reported nine cases of RCM, of

which five underwent cardiac transplant with at least 4 years survival post-transplant.[3] The need for heart transplant was not discussed in the two cases reported due to the non-availability of this management option in Oman.

Conclusion

RCM in children is a rare entity and no cases were reported in Oman until now. Proper symptomatic management is essential in children with RCM and most importantly is timely heart transplant to prevent sudden cardiac death as well as irreversible pulmonary hypertension. In Oman we need to have our own national program for heart transplant to help children with such diseases.

Authors' Contribution

DSH contributed to the conception, acquisition and analysis of data, drafting the manuscript and revising it. NPJ conceptualized the idea, checked and revised manuscript and data, supplied additional data and images, revised manuscript and the first draft. KSAS was involved in the conception of data and revising the manuscript critically. HAR conceptualized the idea with the second author, checked and revised manuscript and data, supplied additional data and revised the first draft. All authors approved the final version of the manuscript.

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Table 1: Laboratory findings

	Case 1	Case 2
C-reactive protein	13	23
Creatine Kinase	Normal	Normal
Ck-MB	32.9 Abnormal	43.2 Abnormal
Troponin-T	Normal	68 Abnormal
Pro-BNP	2079 Abnormal	Not done (No reagent)
TFT	Abnormal TSH (sick euthy)	Normal
ANA	Negative	Negative
Endomyocardial panel	WES negative	CRYAB mutation

COVID-19 swab	Negative	Negative

CK-MB = creatine kinase-myoglobin binding; Pro-BNP = Pro- B-type natriuretic peptide; TFT = thyroid function test; ANA = Antinuclear antibody test; WES= whole exome sequencing; CRYAB= Crystallin alpha B; COVID-19 = Coronavirus disease-2019

Table 2: Electrocardiogram changes

	Case 1	Case 2
P-wave	Peaked and wide, abnormal	Peaked and wide, abnormal
ST-T changes	No	Yes
Axis	Right axis deviation	Normal
RVH	No	No
LVH	No	No
QTc	440 msec	450 msec
Any other abnormalities	Bi-atrial enlargement	Bi-atrial enlargement

RVH = right ventricular hypertrophy; LVH = left ventricular hypertrophy; QTc = corrected QT interval for heart rate

Table 3: Echocardiography findings

	Case 1	Case 2
RA size	Dilated	Dilated
LA size	Dilated	Dilated
LVEF	50%	30-35%
TR	Severe- 15 mmHg	Moderate – 50 mmHg
MR	Not present	Moderate
Lateral wall E’	16 cm/s	6 cm/s
Lateral wall A’	3 cm/s	5 cm/s
Hepatic vein A wave reversal	0.5 m/s	Not available
MV inflow E wave velocity	0.35 m/s	0.77 m/s
MV inflow A wave velocity	0.27 m/s	0.35 m/s
MV E/A	1.31	2.2
Pulmonary vein A wave doppler	Present	Present

MV deceleration time	107 ms	190 ms
Pericardial effusion	Not present	Not present
Impression	Mixed type of left ventricular non-compaction with severe restrictive cardiomyopathy	Mildly hypertrophied infiltrated left ventricle with moderately depressed function.

RA = right atrium; LA = left atrium; LVEF = left ventricle ejection fraction; TR = tricuspid regurgitation; MR = mitral regurgitation; MV = mitral valve

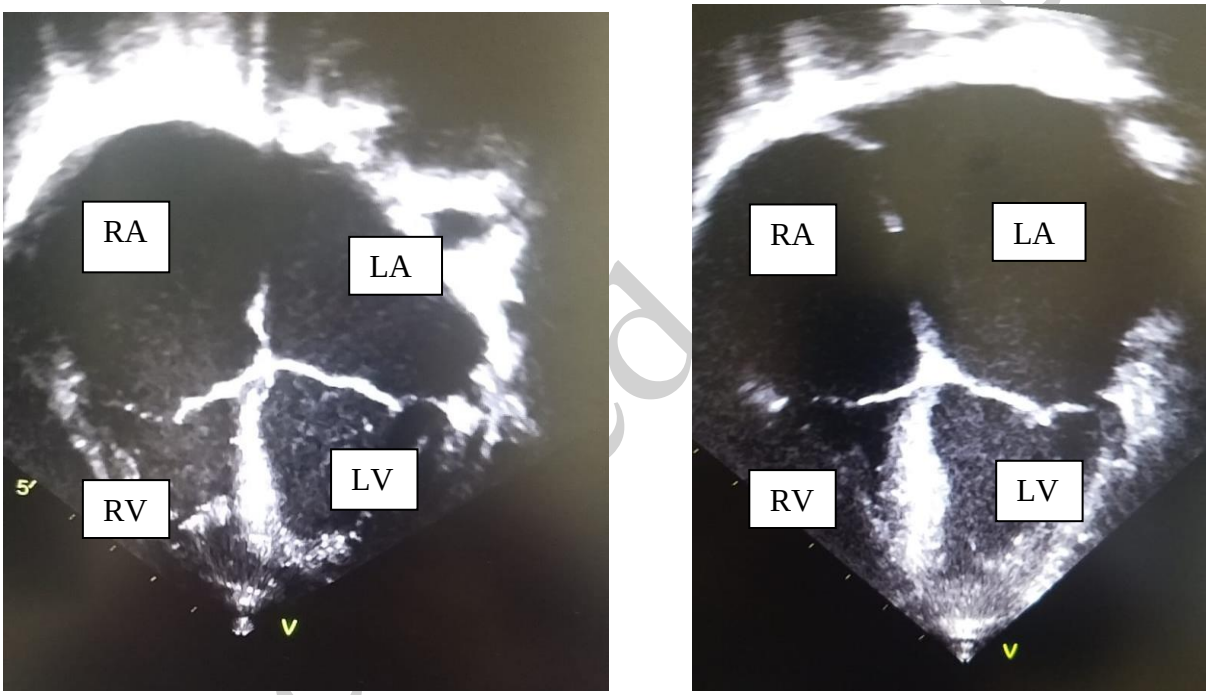

Figure 1: Echocardiography of case 1 (left), and case 2 (right)

RA = right atrium; RV = right ventricle; LA = left atrium; LV = left ventricle