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Pediatric acute heart failure caused by endocardial fibroelastosis masquerading as dilated cardiomyopathy: a case report

Pediatric endocardial fibroelastosis

Abstract

BACKGROUND

Endocardial fibroelastosis (EFE) is a diffuse endocardial collagen and elastin hyperplasia disease of unknown etiology, which may be accompanied by myocardial degenerative changes leading to acute or chronic heart failure. However, acute heart failure (AHF) without obvious associated triggers is rare. Prior to the report of endomyocardial biopsy, the diagnosis and treatment of EFE is highly susceptible to be confounded with other primary cardiomyopathies. Here we report a case of pediatric AHF caused by EFE masquerading as dilated cardiomyopathy (DCM), aiming to provide a valuable reference for clinicians to early identify and diagnose EFE-induced AHF.

CASE SUMMARY

A 13-month-old female child was admitted to hospital with retching. Chest X-ray demonstrated enhanced texture in both lungs and an enlarged heart shadow. Color doppler echocardiography (CDE) showed an enlarged left heart with ventricular wall hypokinesis and decreased left heart function. Abdominal color ultrasonography revealed markedly enlarged liver. Pending the result of the endomyocardial biopsy report, the child was treated with a variety of resuscitative measures including nasal cannula for oxygen, intramuscular sedation with chlorpromazine and promethazine,

cedilanid for cardiac contractility enhancement, and diuretic treatment with furosemide. Subsequently, the child's endomyocardial biopsy report result was confirmed as EFE. After the above early interventions, the child's condition gradually stabilized and improved. One week later, the child was discharged. During a 9-month follow-up period, the child took intermittent low-dose oral digoxin with no signs of recurrence or exacerbation of the heart failure.

CONCLUSION

Our report suggests that EFE-induced pediatric AHF may present in children over 1 year of age without any apparent precipitants, and that the associated clinical presentations are grossly similar to that of pediatric DCM. Nonetheless, it is still possible to be diagnosed effectively on the basis of the comprehensive analysis of auxiliary inspection findings before the result of the endomyocardial biopsy is reported.

Key Words: Endocardial fibroelastosis; Dilated cardiomyopathy; Pediatric acute heart failure; Early identification and diagnosis

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Core Tip: Prior to the report of endomyocardial biopsy, the diagnosis and treatment of endocardial fibroelastosis is highly susceptible to be confounded with other primary cardiomyopathies. Herein, we report a case of pediatric acute heart failure caused by endocardial fibroelastosis masquerading as dilated cardiomyopathy, aiming to provide a valuable reference for clinicians to early identify and diagnose endocardial fibroelastosis-induced acute heart failure.

INTRODUCTION

Pediatric endocardial fibroelastosis (EFE) is a kind of primary infantile cardiomyopathy, also known as endocardial sclerosis[1]. While various theories have been proposed in recent years in relation to the pathogenesis of EFE, the exact etiology of EFE remains unknown heretofore[2]. At present, most scholars believe that it is associated with the immune inflammatory response caused by viral infection[3]. Over 60% of children with onset are younger than one year of age[4]. The clinical manifestations of infants under 6 mo of age is principally acute heart failure (AHF), while the clinical manifestations of infants 6 mo to 12 mo of age is principally chronic heart failure (CHF), and often occurs after respiratory infections[5]. The symptoms and signs of AHF caused by EFE greatly resemble those of the acute exacerbations of dilated cardiomyopathy (DCM) in pediatric patients[5]. However, the treatment options for these two conditions clinically are not exactly identical, and early misdiagnosis may have potentially unintended consequences for the subsequent therapy of the children[6]. More importantly, it is relatively rare for children with EFE over one year of age to develop AHF suddenly without any notable triggers or other directly related underlying diseases[7]. Here we therefore report a case of pediatric AHF caused by EFE masquerading as DCM, in which the child was preliminarily diagnosed as EFE on the basis of critical auxiliary examinations encompassing chest radiography, electrocardiograph and echocardiography alone before the result of the endomyocardial biopsy was available, and a complete clinical remission was achieved with early and correct interventions. By reporting this case, we hope to provide clinicians who are under-resourced for specific subspecialty pathological biopsies with additional empiric references in terms of early screening and differentiating when encountering children with EFE confused with DCM, and to remain vigilant for those children's clinical manifestations.

CASE PRESENTATION

Chief complaints

A 13-month-old female child was admitted to our hospital with retching for 1 wk and worsening for 2 days.

History of present illness

The child had experienced retching without apparent triggers for 1 wk prior to presentation at our hospital, but no vomiting. The child's family denied that the child had a history of fever, rash, cough and expectoration, jaundice, diarrhoea, and trauma. Outpatient blood assays revealed hemoglobin (HGB) 84.00 g/L, C-reactive protein (CRP) 0.30 mg/L, and carbon dioxide combining power (CO_2CP) 15.70 mmol/L. During the course of the illness, the child had poor appetite, poor sleep, fair mental status and reduced urine output, but there was no abnormal exhaust and defecation. The child had no other concomitant symptoms, including any signs of upper respiratory tract infection.

History of past illness

The child was hospitalized in our neonatology unit 1 year ago with a diagnosis of neonatal hyperbilirubinemia (NHB), neonatal bilirubin encephalopathy (NBE), congenital hepatic cyst (CHC), and congenital bilateral renal multiple cysts (CRMC). NHB and NBE recovered favorably after active treatment. CHC and CRMC were treated with conservative observation, and color ultrasonography of the liver and kidneys were conducted every other year. Anemia was detected at 8 mo of age, with a minimum HGB of about 34g/L. After treatment with oral medication and dietary therapy, the maximum HGB was about 80g/L. The child had no previous history of surgery or blood transfusion.

Personal and family history

The child, G1P1, was delivered vaginally at 38^{+2} weeks of gestation, with a birth weight of 2750 g. She was breastfed, with normal growth and developmental milestones and no significant history of medication or food allergies. The child's parents were healthy, and there was no abnormality in the family history.

Physical examination

The child was 74 cm tall and weighed 9.5 kg, with body temperature 36.4°C, pulse rate 150/min, respiration rate 68/min, blood pressure 77/64 mmHg, and poor general status, tachypnea, anemia appearance. Physical examination showed coarse breath sounds in both lungs, low and dull heart sounds, heart rate 150/min, galloping rhythm, a pansystolic grade 3 murmur in the precardiac area, and the lower border of the liver reaching the right pelvic inlet.

Laboratory examinations

The relevant blood tests of the child after admission are illustrated in **Table 1**. A number of laboratory test indicators, including HGB, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and ferritin concentration, were decreased. Biomarkers of heart failure such as N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) were remarkably elevated. No abnormal results were found in urine and stool analyses.

Imaging examinations

Chest X-ray demonstrated enhanced texture in both lungs and enlarged heart shadow, with a cardiothoracic ratio of about 0.62 (**Fig. 1A**). Electrocardiogram (ECG) suggested left axis deviation, paroxysmal supraventricular tachycardia with a heart rate of 150/min and ST-T segment changes. Color doppler echocardiography (CDE) displayed enlarged left heart, thickening of the posterior wall of the left ventricle, minor amounts of mitral regurgitation, ventricular wall hypokinesis and decreased left heart function (**Figs. 1B-D**). Cardiac magnetic resonance (CMR) revealed slight endocardial thickening of the left ventricle, minor thickening of the myocardium, and diffuse motion reduction of the ventricular wall with no apparent delayed enhancement abnormalities (**Figs. 1E and 1F**). Color ultrasonography of the abdomen showed hepatic cyst (size: 0.93 × 0.75 cm), bilateral renal multiple cysts (the largest one size: 1.1 × 1.7 cm) and a markedly enlarged liver with a right oblique diameter of 8.25 cm and an inferior hepatic border

6.32 cm from the right inferior costal arch border of the midclavicular line (**Figs. 2A and 2B**).

FINAL DIAGNOSIS

We arranged emergency consultations with multiple disciplines encompassing respiratory medicine, cardiology, hematology and nursing. According to the clinical symptoms, signs, laboratory examinations, imaging examinations, relevant medical history, age of onset and rapid development of the condition, the child was preliminarily diagnosed with pediatric AHF caused by EFE. And the result of the final endomyocardial biopsy report also confirmed our diagnosis (**Figs. 2C and 2D**).

TREATMENT

As per the standard pediatric advanced life support guidelines, the child was immediately resuscitated and monitored for vital signs, and administered oxygen by nasal cannula (oxygen flow rate: 6 L/min), sedated with chlorpromazine 1 mg/kg and promethazine 1 mg/kg by i.m. injection, enhanced cardiac contractility with 10μg/kg of cedilanid by i.v. push (half of the total amount given for the first time and the remaining amount given in two divided doses, every 6 h), prompted diuresis with 0.1mg/kg of furosemide by i.v. push (given every 6 h), and relieved bronchospasm and reduced myocardial edema with 0.5mg/kg of dexamethasone by i.v. drip[8]. After the above resuscitation measures, the child fell asleep quietly with heart rate 147/min, respiration rate 43/min, and percutaneous oxygen saturation 95-99%, under the bedside monitor. In view of the potential for adverse reactions of either oral or i.v. iron supplementation to adversely affect the child's rescue, we managed her anemia with regular dietary iron supplementation during hospitalization. Day 2 ward rounds, the child was in poor general condition with coarse breath sounds in both lungs, low and dull heart sounds, but stable breathing, and a heart rate of 140/min after activity. Cedilanid was given as a maintenance dose for consolidation therapy, vitamin C was administered intravenously for nourishing the myocardium, and changes in the

condition were closely observed. Day 3 ward rounds, the child's general condition improved with stable respiration, breathing rate 45/min, strong and rhythmic heart sounds, heart rate 120/min. The inferior hepatic border was located approximately 3 cm at the inferior costal arch border of the right midclavicular line, and the hepatomegaly was visibly retracted. Bedside CDE demonstrated that the enlarged left heart began to shrink. After that, low-dose cedilanid was continued to use for maintenance therapy, and monitored the heart rate status. Day 4 ward rounds, the child's condition was relatively stable, with heart rate 105-120/min at rest and percutaneous oxygen saturation above 95%. The relevant blood tests were reexamined and all the laboratory indicators gradually returned to normal. The maintained dose of cedilanid was given again to continue the treatment, and monitored the subtle changes of the condition. Day 7 ward rounds, the vital signs of the child were stable and the breath was slightly tachypnea, with heart rate 116/min and respiration rate 41/min, under the bedside monitor. The inferior hepatic border was located about 2 cm at the inferior costal arch border of the right midclavicular line, and the spleen was not palpated under the left rib. There was no edema in both lower extremities of the child post treatment and the capillary refill time (CRT) was around 2 s. On the same day, the relevant blood tests were reexamined again and a number of laboratory test indicators, encompassing hematocrit, CRP and CO_2CP, returned to normal.

OUTCOME AND FOLLOW-UP

After correct, timely, and effective treatment, the child was discharged on day 7 after admission without any complications. The reexamination result of chest X-ray showed that the enlarged heart shadow was slightly retracted (**Fig. 3A**). Similarly, the computed tomography (CT) reexamination results of thorax and abdomen revealed that the size of enlarged heart was marginally retracted, and the hepatomegaly was visibly retracted (**Figs. 3B and 3C**). After the child was discharged from our hospital, her anemia improved dramatically with a combination of oral drug (ferrous gluconate: 3mg per time, three times one day) and dietary iron supplementation manners. Except for this,

the child took intermittent low-dose oral digoxin (0.05mg per time, once every 12 h) with no signs of recurrence or exacerbation of the heart failure, within a 9-month follow-up period. The timeline of the child's visit is illustrated in **Fig 4**.

DISCUSSION

EFE is one of the important causes of heart failure in infants and toddlers. It occurs in 1/5000 Live births and accounts for 1 to 2% of congenital heart disease, which has an unknown etiology and genetic characteristics, can occur in the absence of cardiac malformations[6,9]. The younger the age of onset of the children with EFE, the worse the prognosis and the higher the mortality[10]. Due to the lack of specificity in the presentation of this disease, it is prone to be confounded with pneumonia and myocarditis and other diseases, so the clinical diagnosis before the result of the endomyocardial biopsy report is difficult, especially when combined with other primary cardiomyopathies that can cause left ventricular enlargement, the clinical presentation of EFE may be masked, with a high risk of missed diagnosis and misdiagnosis[10].

Evidence-based medicine has indicated that AHF caused by EFE has a devastating course and severe prognosis[11]. The gold standard for the diagnosis and differential diagnosis of EFE is the endomyocardial biopsy, however, the biopsy result requires a long waiting time[12]. During this time window, clinicians often first need to refer to chest radiographs, ECGs, CDEs and related laboratory examinations for initial diagnosis and early patient management, which is a great test for clinicians' personal competences and experience levels. Currently, no practical guidelines on the diagnosis and treatment of EFE prior to the tissue biopsy result have been released internationally by national heart associations worldwide. The discrimination of pediatric AHF caused by EFE from other diseases with similar clinical symptoms and manifestations is therefore very challenging, especially for DCM in infants and young children[13].

Children younger than 1 year of age or even younger with primary EFE are more likely to be exactly diagnosed according to the age distribution of the onset of pediatric heart diseases[17-19]. Yet, in rare-onset children older than 1 year of age, the manifestation of EFE's cardiac imaging examinations are almost identical to those of early onset DCM in infants and toddlers[20]. Both show a sudden dilatation of a single heart cavity (*e.g.*, the left ventricle) on chest X-ray or chest CT. On a more accurate CDE inspection, both also exhibit the same ventricular wall hypokinesis, varying degrees of ventricular wall thickening, cardiac valve regurgitation, and left heart dysfunction. And more important, the blood-related tests of both present with assay indicators of AHF without any specificity. These things together make it easy for pediatric AHF caused by EFE to be masqueraded as DCM[10].

In our case, this 13-month-old female child suddenly developed AHR without any triggers and without any history of infection, cardiac malformation, and other underlying cardiovascular disease. This is relatively rare in clinical practice, as many studies suggest that respiratory infections and congenital cardiovascular malformations are important triggers and potential initiators in the development of AHF caused by EFE[10]. We had considered pediatric DCM before the available endomyocardial biopsy result was returned, yet the echocardiographic findings just showed a diffuse and uniform slight thickening of the left ventricular endocardium with echo dense and enhanced, and a clear demarcation between ventricular endocardium and myocardium, a slight thickening of the myocardium, only a small amount of mitral regurgitation, a left ventricular end-diastolic dimension (LVEDd) of 42 mm (<50 mm). In parallel, both bright-blood T_1-weighted image (T_1WI) sequences and black-blood T_2-weighted image (T_2WI) sequences of the CMR examination of the child demonstrated a general thickening of the endocardium. In fact, for DCM, the possible thickening of the ventricular wall will not appear on the endocardium, but rather more on the thickening of the myocardium, and there are no non-functional fibrotic changes similar to EFE with this thickening. In such cases, when DCM presents with AHF, it is possible that the

indicators of left ventricular systolic function on the CDE may not be much decreased. Furthermore, though the ECG manifestations of both DCM and EFE in infants and toddlers are left ventricular high voltage, poor R-wave progression, ST-T segment changes, and various different arrhythmias, the primary characteristics of the former are typically atrial tachycardia and atrial fibrillation. These are all distinctly different from EFE. Of note, the bedside CDE on the third day of admission suggested that the dilated left heart had begun to show retraction, but this is almost impossible in DCM. Because despite the fact that DCM can be relieved, it is difficult to reduce the size of the heart to normal. Combined with the child's age of onset, family history, and the findings of consultations with physicians from different departments, we unanimously agreed that EFE should be given a higher diagnostic priority. With more evidence pointing to EFE, we made a preliminary diagnosis of pediatric AHF caused by EFE prior to the result of the tissue biopsy was reported, which bought valuable time for early timely and correct intervention in the progression of the child's disease. More importantly, both the rapid improvement of the child's condition after treatment and the result of the endomyocardial biopsy report ultimately confirmed that our judgment was correct.

Unfortunately, no directed therapeutic approach for EFE is known since the rarity of the condition[21]. Yet, recovery of the enlarged heart and lost cardiac function in children with EFE is possible, and current clinically recommended treatment typically follows a standardized and vigorous decongestive therapy based on cardiac glycosides[22]. The child followed such a treatment principle from admission to the 9-month follow-up cut-off point after discharge, and this hospital and domiciliary treatment has helped her well to maintain the sustainability of the decongestive therapy. In recent years, long-term follow-up studies have shown that bioimmunotherapy increases the clinical benefit of children with EFE and helps to improve endocardial hyperplasia and fibrosis[23]. Given the risk of future infection of the child's hepatic and renal cysts and the underlying physical conditions, there was no opportunity to apply steroid

hormones or other biological immunomodulators to her. However, we still recommend the use of biological immunomodulators for those children with EFE who have indications, because they may improve the prognosis of heart failure. Compared with EFE, while DCM is also treated in the acute exacerbation phase using a heart failure management approach, it is generally managed with long-term diuretics, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers and beta-blockers to control its progression of CHF and ventricular remodeling due to the irreversibility of cardiac enlargement and decline in cardiac function[24]. Additionally, though bioimmunotherapy for adult DCM seems to benefit a proportion of patients, to date such treatments have not raised sufficient promise for pediatric DCM, and there is no evidence that steroid hormones use reduce mortality and morbidity in children with DCM[25]. As a result, the treatment regimens for EFE and DCM in in infants and toddlers are not always identical, and early misdiagnosis improper treatment may have potentially unintended consequences for the children's prognosis.

In infant and young childhood, EFE frequently presents with DCM and unfavorable progression, which makes it difficult for clinicians to distinguish these two diseases[6,14]. While the case we report is successful in differentiating EFE from DCM prior to the pathology report result, this is based more on extensive clinical work experience[15,16]. Limited by the objective one-sidedness of individual information, the early identification of such pediatric AHF caused by EFE masquerading as DCM still requires more clinical medical record information and data support.

CONCLUSION

Here, we report a case of pediatric acute heart failure caused by endocardial fibroelastosis masquerading as dilated cardiomyopathy, which was accurately identified early in the course of the disease, for which we demonstrate that a primary diagnosis for endocardial fibroelastosis before the result of the endomyocardial biopsy

is entirely possible. We hope that our report will give clinicians more decision support and attract sufficient attention when diagnosing similar diseases.

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