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(CASE REPORT)

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Primary idiopathic endocardial fibroelastosis in a four-month-old infant: Case report and brief literature review

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Abstract

Primary idiopathic endocardial fibroelastosis (pEFE) is a rare infantile cardiomyopathy characterized by diffuse thickening of the ventricular endocardium by collagen and elastic tissue, leading to severe left ventricular dysfunction. This report describes a four-month-old male infant who presented with a three-week history of feeding difficulties, failure to thrive, and respiratory distress, which were initially misdiagnosed as gastroesophageal reflux. An acute episode of perioral cyanosis prompted emergency evaluation revealing profound left ventricular dilation and a severely reduced ejection fraction of 28%. Following the exclusion of anomalous left coronary artery from the pulmonary artery (ALCAPA) and other secondary causes via echocardiography and cardiac magnetic resonance imaging, an endomyocardial biopsy confirmed the diagnosis of pEFE.

The infant was managed with intensive anti-heart failure pharmacotherapy, including captopril, carvedilol, furosemide, and spironolactone, alongside aggressive nutritional support. This medical regimen resulted in significant clinical improvement, with the ejection fraction recovering to 55% at the 18-month follow-up, despite persistent endocardial echogenicity.

This case underscored the critical importance of maintaining a high index of suspicion for underlying cardiomyopathies in infants presenting with persistent feeding difficulties and respiratory symptoms, as early diagnosis and aggressive medical management can yield excellent long-term outcomes and reverse profound cardiac dysfunction in primary endocardial fibroelastosis (EFE).

Keywords: Primary idiopathic endocardial fibroelastosis; Infantile cardiomyopathy; Collagen and elastic tissue; Left ventricular endocardial thickening; Heart failure

1. Introduction

Endocardial fibroelastosis (EFE) is a rare form of pediatric cardiomyopathy characterized by the deposition of elastic and collagen fibers in the subendothelial layer of the endocardium, leading to progressive heart failure. [1] EFE primarily presents in infants and children, usually within the first year of life. [2] It most commonly affects infants with other cardiac anomalies such as hypoplastic left heart syndrome, aortic stenosis, and atresia. [3] However, the idiopathic form is not associated with concurrent cardiac anomalies. Etiology remains unclear, but researchers suggest possible genetic, viral, or autoimmune mechanisms. [2] Clinically, EFE presents with nonspecific signs of heart failure, including

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gallop rhythm, hepatosplenomegaly, tachypnea, failure to thrive, and raised Jugular venous pressure. [1,2] Echocardiography remains the main diagnostic modality, with identification of the characteristic thick, echogenic endocardium. [2] Management of EFE is primarily focused on symptomatic treatment, as there are no disease-specific therapies. [1] Some studies have shown that managing flow may be an effective treatment for EFE. [4]

We present a case of idiopathic EFE in a 4-month-old male with no prior cardiac history who presented with progressive feeding intolerance, intermittent tachypnea during feeds, failure to gain weight, grunting respirations, diaphoresis with feeds, and an episode of perioral cyanosis. This case highlights the diagnostic complexity of idiopathic EFE and contributes to the limited literature on idiopathic EFE.

2. Case Presentation

2.1. Clinical presentation

A previously healthy 4-month-old male infant presented with a three-week history of poor feeding, intermittent tachypnea during feeds, and failure to gain weight. His parents noted occasional grunting respirations and excessive sweating with feeding over the past week. One day prior to admission, he developed perioral cyanosis and extreme irritability. The infant had been managed with standard formula and anti-reflux measures without improvement. He had no prior hospitalizations or known cardiac disease. The family history was unremarkable for congenital heart disease or cardiomyopathies. A pediatrician twice diagnosed reflux and prescribed thickening of feeds, which transiently reduced vomiting but did not improve respiratory symptoms or weight gain. The acute episode of cyanosis and lethargy prompted an emergency department visit.

2.2. Physical examination and initial investigations

Physical examination revealed a tachypneic (respiratory rate 65/min) and tachycardic (heart rate 170/min) infant with normal oxygen saturation on room air. Weight was below the 5th percentile. Cardiovascular examination showed a quiet precordium, an audible S3 gallop, and a soft apical systolic murmur without hepatosplenomegaly. Peripheral pulses were weak. There was no cyanosis at rest. Family history was negative for sudden death or cardiomyopathy.

Laboratory studies showed mild elevation of B-type natriuretic peptide (850 pg/mL) and normal electrolytes, thyroid function, and metabolic screen. Chest radiography revealed cardiomegaly with a globular heart shape and pulmonary venous congestion. Electrocardiography demonstrated left ventricular hypertrophy with deep Q waves in leads V5-V6 and left atrial enlargement. Echocardiography showed a dilated left ventricle with severely reduced systolic function (ejection fraction 28%), thickened and bright endocardium, and normal coronary arteries. Cardiac MRI confirmed diffuse left ventricular endocardial thickening with delayed endocardial enhancement.

Clinical differential diagnosis included dilated cardiomyopathy (myocarditis, metabolic), ALCAPA, and primary endocardial fibroelastosis (EFE). Radiologic differentials included EFE versus hypertrophic cardiomyopathy with endocardial involvement.

2.3. Multidisciplinary tumor board discussion

After initial stabilization with diuretics, afterload reduction, and inotropic support, the pediatric cardiology, pediatric pathology, cardiothoracic surgery, and genetics teams convened. The discussion centered on distinguishing primary idiopathic EFE from secondary causes, particularly ALCAPA, which requires surgical correction. Given normal coronary origins on echocardiography and MRI, ALCAPA was excluded. The team debated whether to perform endomyocardial biopsy to rule out occult myocarditis or storage disease. Consensus favored proceeding with biopsy due to the absence of a clear underlying etiology. The team agreed that primary EFE was the most likely diagnosis.

Management decisions included initiating standard heart failure pharmacotherapy (captopril, carvedilol, furosemide, spironolactone) and planning for endomyocardial biopsy and possible surgical endocardectomy if medical therapy failed. The team recommended genetic counseling and comprehensive metabolic testing. Nutritional optimization with high-calorie formulas and nasogastric tube feeding was initiated.

2.4. Pathology, ancillary studies, and final diagnosis

Endomyocardial biopsy from the left ventricle revealed dense fibroelastic tissue thickening of the endocardium with overlying normal myocardium. Hematoxylin and eosin staining showed acellular collagen bundles interspersed with elastic fibers. Verhoeff-van Gieson staining highlighted abundant black-purple elastic fibers within the thickened

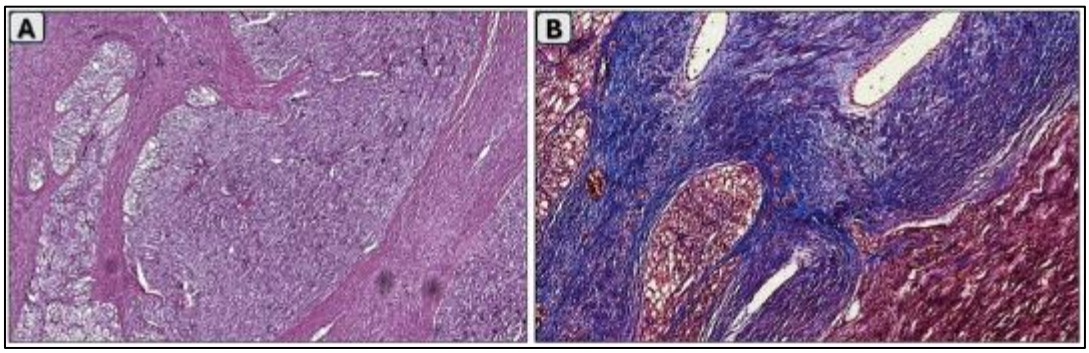
endocardium, diagnostic of endocardial fibroelastosis, and trichrome staining showed prominent scarring. (**Figure 1 A, B**) Immunohistochemistry (IHC) was negative for inflammatory infiltrates (CD3, CD68) and viral antigens.

Molecular studies using PCR for cardiotropic viruses (enterovirus, adenovirus, parvovirus B19, HHV-6) were negative. Whole-exome sequencing revealed no pathogenic variants in genes associated with primary EFE (TAZ, G4.5) or mitochondrial cardiomyopathies. Metabolic studies, including plasma amino acids, urine organic acids, and acylcarnitine profile, were normal. These findings confirmed the diagnosis of pEFE.

2.5. Treatment, outcome, follow-up, and patient condition after 18 months

The patient received intensive heart failure therapy with captopril (0.5 mg/kg per dose three times daily), carvedilol (0.1 mg/kg twice daily, increased to 0.4 mg/kg twice daily), furosemide (1 mg/kg twice daily), and spironolactone (1 mg/kg daily). High-calorie formula delivered through a nasogastric tube supported adequate weight gain. After three weeks of medical treatment, he was discharged home.

At the 3-month follow-up, left ventricular ejection fraction had improved to 40%, although endocardial thickening persisted. By 6 months, he was asymptomatic, with an ejection fraction of 50% and normal growth. At 18 months, he was thriving, weighing at the 25th percentile, and met all developmental milestones. Echocardiography showed mild residual left ventricular enlargement (z-score +2) and an ejection fraction of 55%, with persistent but stable endocardial echogenicity. Heart failure therapy was reduced to captopril and carvedilol alone. He continued annual cardiology follow-up and had no further hospitalizations.



1A**:** Intermediate-power H&E view showing dense fibroelastic endocardial thickening overlying normal myocardium (×40); 1B**:** Trichrome stain demonstrating prominent scarring with acellular collagen bundles interspersed with elastic fibers.

Figure 1 Microscopic features of endocardial fibroelastosis (EFE)

3. Discussion

3.1. Background (History, epidemiology, risk factors, and WHO classification):

An abnormal thickening of the endocardium characterizes endocardial fibroelastosis (EFE) due to a build-up of elastic and fibrous tissue. The World Health Organization (WHO) categorizes EFE as a form of restrictive cardiomyopathy, specifically under the non-inflammatory subcategory. It almost exclusively affects infants and small children. [5] Early observers in the 19th and 20th centuries hypothesized that the condition was caused by intrauterine inflammation of undetermined etiology. [6] EFE was officially introduced into medical literature in the mid-20th century, where it was frequently diagnosed as a primary rare cardiomyopathy in infants and children with an unexplained severely dilated left ventricle and congestive heart failure. [6,7] Starting in the early 2000s, the terminology associated with the condition transitioned to dilated or restrictive cardiomyopathy, and the consensus shifted toward EFE being viewed as a response to genetic factors rather than a standalone condition. [8]

EFE is generally classified as either primary (idiopathic) or secondary. Secondary EFE (sEFE) has several etiological causes, including genetic conditions such as Barth Syndrome or X-linked EFE, viral infections particularly mumps and coxsackievirus B, or congenital heart defects such as hypoplastic left heart syndrome (HLHS) or congenital aortic stenosis. [5,8,9] The primary or idiopathic form is sporadic, affecting approximately 1 in every 5000 live births. It primarily affects infants, with most cases presenting between 2 and 12 months of age and generally affecting both sexes equally. [5,8] Primary EFE (pEFE) is often clinically indistinguishable from idiopathic dilated cardiomyopathy, so while

pEFE is considered exceptionally rare, pathology reviews have found that it may account for up to 25% of pediatric heart transplants originally attributed to dilated cardiomyopathy, which suggests an element of underdiagnosis. [9,10]

3.2. Pathogenesis, Pathophysiology

Some investigators reported that EFE is mainly caused by abnormal endothelial-to-mesenchymal transition (EndMT) of endocardial cells. [8] This is driven by hypermethylation of the BMP5 and BMP7 promoters, which suppress transcription of endogenous EndMT inhibitors and leads to unopposed TGF-β-driven fibrosis. [8] Endocardial endothelial cells undergo this transition, becoming mesenchymal cells and enabling deposition of collagen and elastin. [8,11] Additional contributing factors include left ventricular dilation with stagnant flow, viral-induced myocardial injury, and genetic factors, which are found in most primary EFE cases. [12,13,14] Genetic associations currently described are Nebulette mutations, X-linked Barth syndrome, 16p11.2 microdeletions, and various autosomal recessive forms. [15,16] Recent studies suggest these combined factors cause the subendocardial fibroelastic tissue seen in idiopathic EFE. [17]

Active EndMT is identified on histopathology by the presence of both endothelial markers (CD31/VE-cadherin) and mesenchymal markers (α-SMA, vimentin, FSP-1). [3] Several histochemical stains and techniques are used to evaluate EFE, including H&E, Masson's trichrome, Russell-Movat's pentachrome, picrosirius red, Verhoeff-Van Gieson, Hart's stain, Weigert's Resorcin-Fuchsin, and transmission electron microscopy. [18] The most common methods, H&E and Masson's trichrome, show endocardial thickening and extensive blue-staining collagen deposition, while underlying myocardial architecture is preserved. [18]

3.3. Comparative Analysis of Our Case with Existing Literature.

pEFE has historically been associated with a poor prognosis, frequently progressing to refractory heart failure or sudden cardiac death if unrecognized. [10,19] Consistent with the literature, our patient presented within the first six months of life with signs of decompensated heart failure, which initially masqueraded as common pediatric issues such as feeding intolerance. [2]

Unlike secondary EFE, which is often linked to structural anomalies like hypoplastic left heart syndrome or ALCAPA, primary EFE presents without such defects but shares a similar phenotypic picture of dilated cardiomyopathy (DCM). [20] Recent studies have highlighted that while EFE is morphologically distinct from idiopathic DCM, demonstrating significant endocardial thickening and restrictive physiology, the initial clinical manifestations are nearly indistinguishable. [19]

In contrast to cases requiring heart transplantation or those resulting in fatality [10,21], our patient demonstrated a remarkable recovery of ventricular function following early initiation of angiotensin-converting enzyme inhibitors and beta-blockers. This aligns with contemporary observations that aggressive, early medical management can induce favorable remodeling and significantly improve ejection fraction in infantile cardiomyopathies [22], distinguishing modern survival trajectories from the historical natural history of the disease.

4. What Have We Learned from This Case?

This case reinforced several critical clinical insights regarding the evaluation of infants with nonspecific symptoms. Foremost, it highlighted the diagnostic pitfall of attributing persistent feeding difficulties, failure to thrive, and tachypnea solely to common conditions like gastroesophageal reflux. Clinicians must recognize excessive sweating during feeds and unexplained tachypnea as red flags warranting prompt cardiovascular evaluation.

Diagnostically, while echocardiography remains the first-line modality, cardiac magnetic resonance imaging was invaluable for delineating the characteristic delayed endocardial enhancement and for excluding structural anomalies such as ALCAPA. [23] Furthermore, the case demonstrated the diagnostic utility of endomyocardial biopsy in ambiguous infantile cardiomyopathies, definitively separating primary EFE from myocarditis or metabolic storage diseases.

From a management perspective, this case challenged the historically grim prognosis of pEFE, illustrating that profound left ventricular dysfunction (ejection fraction of 28%) is not irreversible. It reinforced the existing knowledge that early, aggressive medical therapy combining afterload reduction and beta-blockade, coupled with rigorous nutritional support, can facilitate remarkable myocardial recovery and alter the disease trajectory. Continuous surveillance remains imperative, as endocardial thickening often persists despite functional normalization.

Abbreviations

- Primary idiopathic endocardial fibroelastosis (pEFE)
- Enocardial fibroelastosis (EFE)
- Anomalous left coronary artery from the pulmonary artery (ALCAPA)
- Immunohistochemistry (IHC)
- Endothelial-to-mesenchymal transition (EndMT)

5. Conclusion

Primary idiopathic endocardial fibroelastosis remains an underappreciated and potentially fatal cause of infantile heart failure. We present this case to emphasize that pEFE can be successfully managed medically when identified promptly, adding to the growing body of evidence that severe initial ventricular dysfunction in infants is reversible. By detailing the clinical journey from a misleading presentation of reflux to a definitive biopsy-proven diagnosis and subsequent functional recovery, this report provided the medical community with a vital reminder to consider primary cardiomyopathies in infants with refractory feeding issues. Ultimately, it underscored the value of a multidisciplinary diagnostic approach and the efficacy of standard heart failure regimens in achieving excellent long-term outcomes in primary endocardial fibroelastosis.

Compliance with ethical standards

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- Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might be interested in the submitted work.

Statement of informed consent

Informed consent for the publication of this case was obtained from the patient.

Data access statement

All relevant data are included in the paper.

Author contributions

All authors contributed equally to producing this manuscript.

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