Cardiovascular Pathology 42 (2019) 1–3

Contents lists available at ScienceDirect

Cardiovascular Pathology

Original Article

Flow disturbances and progression of endocardial fibroelastosis — a case report

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ARTICLE INFO

Article history:
Received 9 April 2019
Received in revised form 26 April 2019
Accepted 30 April 2019

Keywords:
EFE
HLHS
EndMT

ABSTRACT

Endocardial fibroelastosis (EFE) is described as thickening of the endocardium and is associated with hypoplastic left heart syndrome (HLHS). The stimulus for EFE and the mechanism for recurrence and/or progression need to be investigated. In this report, we describe the case of a 4-year-old HLHS patient who underwent several surgeries with EFE resections due to recurrence of EFE. EFE recurrence was associated with flow disturbances due to valvar defects. At her latest follow-up 7 months after the last surgery, competent valves and no EFE were identified on all imaging study.

1. Introduction

Thickening of the left ventricular (LV) endocardium termed endocardial fibroelastosis (EFE) is associated with hypoplastic left heart syndrome (HLHS) and is thought to be linked to the inability of the LV to grow and develop normally. We have previously established that endocardial endothelial cells are the origin of EFE which is derived through a mechanism called endothelial-to-mesenchymal transition (EndMT) [1]. It is still unclear what stimulates EndMT, but hemodynamic changes may play a role in this pathological process.

1.1. Case presentation

We present the case of a 4-year-old female patient who was prenatally diagnosed with HLHS and was transferred to Boston Children's Hospital (BCH) shortly after birth for staged palliation. The first postnatal echocardiogram and magnetic resonance imaging (MRI) confirmed mitral (MV) and aortic valve (AV) stenosis with restrictive, thickened leaflets, moderately sized atrial septal defect with left to right shunt. A bright thick layer of EFE covering the endocardial surface of the LV was described.

1.1.1. First surgery

Two days after birth, stage-I palliation was performed with a 5-mm Sano-shunt and atrial septectomy. The 5-month-old patient was evaluated for the second staged operation, and echocardiographic and MRI confirmed EFE. LV end-diastolic volume (EDV) was measured as 8.4 ml/m$^{2.}$

1.1.2. Second surgery

The Sano-shunt was replaced by a Glenn anastomosis, accompanied by resection of EFE from the LV cavity.

At 17 months old, symptoms reoccurred and also EFE on echocardiography and MRI. By MRI, LV-EDV was 24.5 ml/m^2, and at catheterization, the LV-EDP measured 11 mmHg and mean LA pressure was 22 mmHg.

1.1.3. Third surgery

The MV and AV were repaired and EFE was resected from the LV. Intraoperatively, it was noted that motion of the MV leaflets was restricted by an introleaflet membrane, most probably EFE.

At 2 years and 3 months of age, despite successful repair, valvar disease progressed, and MRI follow-up showed gadolinium enhancement in the LV involving the MV. However, the LV-EDV had increased to 32 ml/m^2 with an ejection fraction of 75%. The LA pressure at catheterization was 18 mmHg with an LV-EDP of 12 mmHg.

1.1.4. Fourth surgery

EFE was resected from the LV and the posterior leaflet of the MV, which was attached to the LV free wall. MV and AV both necessitated

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https://doi.org/10.1016/j.carpath.2019.04.004
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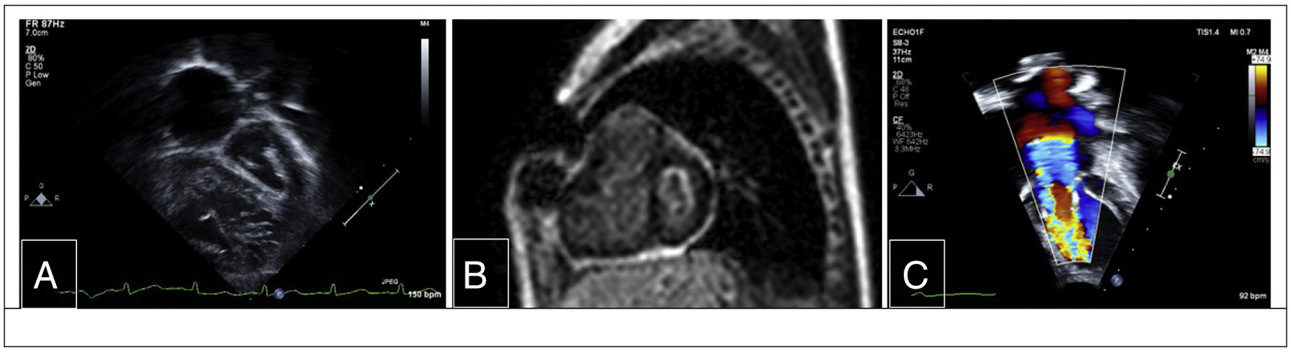

Fig. 1. Echocardiography shows thickened endocardium with gadolinium enhancement on MRI, indicative of EFE (A and B). On echocardiography, a jet across the Melody valve aiming at the septal surface of the LV where EFE tissue was predominantly resected (C).

valvuloplasty due to restricted motion and thickened leaflets. A Blalock–Taussig shunt was added to augment pulmonary venous return and, hence, flow across the MV and into the LV.

One year after surgery at 3 years, 5 months old, echocardiography and MRI showed moderate MV stenosis and regurgitation, but extensive gadolinium-enhancement was present with improvement of LV-EDV to 45 ml/m^2 and an LV-EDP of 9 mmHg on catheterization.

1.1.5. Fifth surgery

Due to sufficient catch-up growth of the LV, conversion to biventricular circulation was performed with take-down of the Damus–Kaye–Stansel and Blalock–Taussig shunts and attachment of the RV directly to the pulmonary arteries. EFE was resected from the LV, and the MV was replaced with a 16-mm Melody valve.

At 4 years of age, the patient developed symptoms of tachypnea, cough, and cyanosis. On echocardiography, the mean gradient across the Melody valve was 7 mmHg, and the LVOT peak gradient was 36 mmHg. At catheterization, the LV-EDP was 26 mmHg, and MRI showed an EDV of 37.7 ml/m^2 with gadolinium enhancement at the apical and basal septum (Fig. 1A–C).

1.1.6. Sixth surgery

After 3 months at 4 years and 2 months old, without symptomatic improvement and with unchanged structural and hemodynamic findings on imaging studies, the Melody valve was replaced with a 19-mm Epic porcine valve and the AV was repaired. EFE was resected from the septal surface and posteriorly.

At last follow-up at 4 years and 10 months of age, the patient's symptoms had significantly improved. Echocardiography showed normal prosthetic valve function, and normal LV size and systolic function. At catheterization, LV-EDP was 12 mmHg with a cardiac index of 3.3 L/min/m^2. LA pressure was 14–16 mmHg with half systemic pulmonary artery pressure.

1.2. Comment

EFE is described as fibroelastic thickening of the endocardium mainly localized in the LV, diagnosed in 1.6% of newborns' pathological specimens with heart disease [2]. It is linked to different underlying structural diseases and most commonly to HLHS [3]. Following analysis of EFE from 27 HLHS patients, we identified a potential root cause of EFE in aberrant EndMT affecting the endocardium of the LV [1]. EndMT is a physiologic process during the development of heart valves, but the stimulus for pathologic EndMT in HLHS is unknown. In association with HLHS, many potential triggers have been hypothesized, but clinical observations and animal models point toward flow disturbances exposing endocardial cells to alterations in shear stress [4].

BCH advocates an approach toward LV recruitment in HLHS to support the systemic circulation which entails resection of EFE tissue. Resection of EFE is technically feasible and results in catch-up growth of the LV indicated by an increase in LV-EDV, but many patients experience regrowth of EFE [5,6]. Furthermore, as indicated by this case, as the patient grows older, EFE switches to an infiltrative growth pattern affecting the myocardium. Until now, no underlying reason for reoccurrence and infiltrative growth patterns has been described [5]. With multiple EFE tissue samples from consecutive surgical resections available in this patient, we could show that EFE growth was directly associated with flow disturbances across the mitral valve. Flow disturbances due to mitral valve stenosis followed by a malpositioned Melody valve were associated with alterations of endocardial tissue in this area. Furthermore, despite repeated EFE resections but without resolution of the pathological flow pattern,

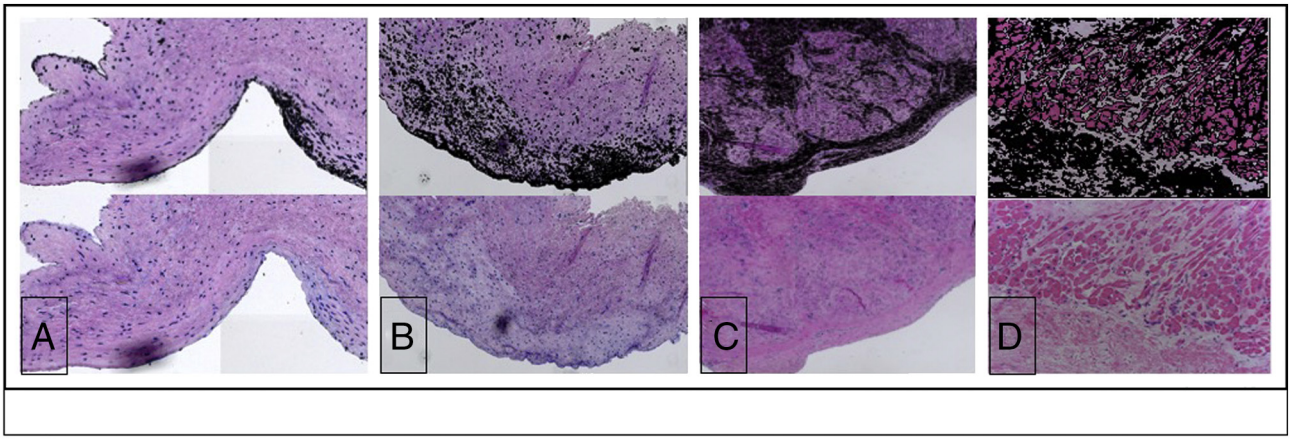

Fig. 2. Hematoxylin and eosin staining of EFE tissue from four different surgeries (A=first, B=second, C=fourth, D=sixth); bottom: original stain and top: emphasized by black labeling. With each resection, EFE takes on a more infiltrative growth pattern into the underlying myocardium.

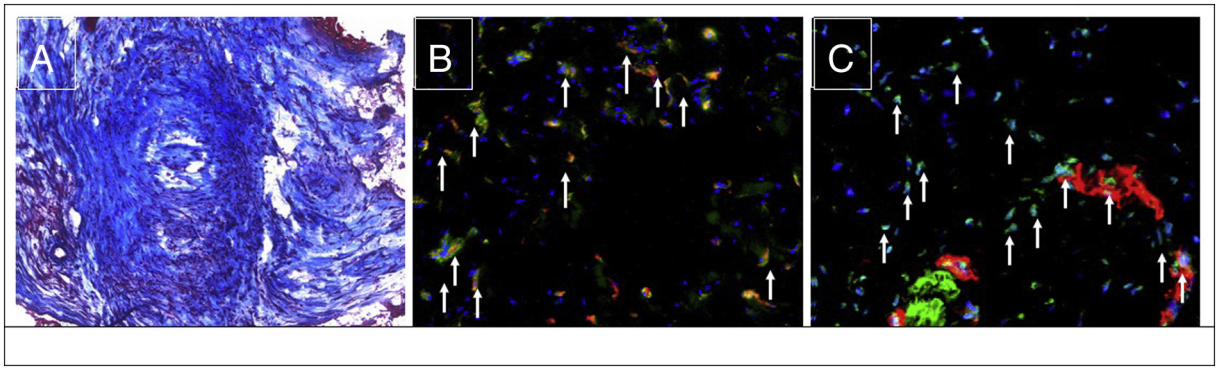

Fig. 3. EFE tissue from the last resection: (A) Masson's Trichrome stain: Collagen (blue) dominates EFE. (B) Double staining of endothelial cells with an endothelial marker (red=CD31) and a mesenchymal marker (green=alpha-SMA) is indicative of active EndMT (arrows). Nuclei are stained in blue (DAPI). (C) Double-stained nuclei (DAPI=blue) of endothelial cells (red) and TWIST (green), a transcription factor regulating EndMT, are confirmation of active EndMT (arrows).

EFE regrew and changed from a subendocardial growth pattern to more infiltrative growth into the myocardium as the patient grew older and flow disturbances across the MV persisted (Fig. 2A–D). Infiltrative growth is associated with elevated LV-EDP, but growth of the once diminutive LV is maintained indicated by increasing LV-EDV.

Plasticity of endothelial cells allows for adaptation to physiologic and pathologic processes whereof the latter is represented by EndMT. It is well known that flow disturbances in the vasculature generate a microenvironment supportive of EndMT [7,8]. Our case study now supports the idea that flow disturbances play a role in endocardial EndMT as well (Fig. 3A–C). Through the course of disease progression, EFE formation was directly associated with flow disturbances across the MV. With definitive repair of the valve, thickening of the endocardium indicative of EFE has not reoccurred 7 months following the last surgery.

Declaration of competing interest

None.

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