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Case Report

Long Term Outcome and Pathological Characterization of Extracellular Matrix for Tricuspid Valve Repair

Elisa Gastino[1]*, Marny Fedrigo[2], Annalisa Angelini[2] and Massimo A Padalino[1]

[1]Pediatric and Congenital Cardiac Surgery, Department of Cardiothoracic and Vascular Sciences, and Public Health, University of Padova, Italy

[2]Cardiovascular Pathology, Department of Cardiothoracic and Vascular Sciences, and Public Health, Italy

***Corresponding Author:** Elisa Gastino, Pediatric and Congenital Cardiac Surgery, Department of Cardiothoracic and Vascular Sciences, and Public Health, University of Padova, Italy.

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Abstract

Porcine small intestinal submucosa extracellular matrix (SIS-ECM) is a relatively novel tissue substitute used in cardiovascular applications. We investigated the long term biological reaction and remodeling of SIS-ECM substitute in a 53 years-old woman who underwent heart transplant after multiple reoperation after repair for complete atrioventricular septal defect.

Keywords: Porcine Small Intestinal Submucosa Extracellular Matrix (SIS-ECM); Quality; Valve

The quality of tissue substitutes, whether biological or synthetic [1], is a key element for a durable effective valve repair which includes leaflet reconstruction or extension [2,3]. Porcine small intestinal submucosa extracellular matrix (SIS-ECM) is a biological tissue substitute which has been introduced as an alternative to conventional pericardial patches, to possibly improve long-term outcomes after cardiac repair [4]. Such material has been reported for multiple types of intracardiac repair of congenital heart disease, including an alternative replacement of severely dysfunctional tricuspid valve (TV) in infants [5].

Recent clinical data, although inconclusive, have raised concerns with respect to its growth, regeneration and immune-stimulatory properties [6,7].

We report on the late histologic tissue characterization of TV septal leaflet replacement with SIS-ECM, in a patient who later on underwent heart transplant.

Case Report

A 53-years-old woman with a history of multiple reoperations for complete atrioventricular septal defect (AVSD) was admitted in our unit with advanced heart failure and severe tricuspid regurgitation.

The patient had undergone complete double patch repair at 14 years of age, a left AV valve repair at 17 years, and at 45 years she was referred to our center for residual severe regurgitation of both AV valves. In the latter admission, she underwent left AV valve replacement with mechanical prosthesis SJM 27 mm, and a right AV valve repair with anterior leaflet patch reconstruction. In particular, the tricuspid valve whose annulus was extremely dilated, was severely regurgitant because of tethering of the septal leaflet and adhesion to the interventricular septum. After a De Vega annuloplasty, the septal leaflet was completely reconstructed

with an artificial triangular shaped flap of SIS-ECM. After repair, there was no significant regurgitation at hydrodynamic saline test. After cardiopulmonary bypass discontinuation, a postprocedural trans-esophageal echocardiography showed trivial right AV valve regurgitation, and mobile prosthetic leaflet.

After discharge on POD 14, with oral treatment with diuretics, aldactone, sotalolo, lanoxin, bosentan and coumadin, the patient was well for several years. However, she gradually developed worsening dyspnea, orthopnea and paroxysmal nocturnal dyspnea, and ascites. An abdominal CT scan showed chronic liver disease on a cardiogenic basis. Echocardiographic assessment showed progressive biventricular dilation and dysfunction, mild aortic regurgitation, and progressively severe right AV valve regurgitation (Figure 1, Panel A, Panel B). For these reasons, after hospital admission in ICU, where she required prolonged dialysis and inotropic support, she was listed for heart transplantation. After 8 years from last surgery, she underwent heart transplantation. The pathological examination of native heart removed at the time of transplantation showed a negative remodeling of both ventricles after multiple surgical interventions for common AV septal defect (Figure 2 Panel B). Both atria were severely dilated, and a huge enlargement of the coronary sinus was noticed. The septal patches were calcified. (Figure 2 Panel B). The right ventricle was hypertrophic and the interventricular septum displaced toward the left ventricle (Figure 2 Panel C). Figure 2 Panel D shows left AV bioprosthesis. The reconstructed TV was analyzed accurately. The Ex vivo X-Ray of the heart showed the distribution of calcifications within the SIS-ECM patch and the tendinous cords. (Figure 2 Panel D white asterisk). It was evident that the SIS-ECM patch had been sutured to the native septal leaflet remnant of the right AV valve attached to the septum (Figure 3 Panel A, red line). The histology sections were conducted perpendicular to the A-V valve sulcus and the position of patch in the leaflet of TV was evident. The patch position was marked with a dotted line in the three panels (b, c, d) of figure 3. The native valve was dysplastic and major histopathology feature was characterized by fibrosis remodeling (figure 3 Panel c), surrounding the SIS-ECM patch (see the dotted blue line). The SIS-ECM patch was intact, completely inert, without degenerating or remodeling evidence; no inflammatory cells were present, while focal aggregates of lymphocytes were detected in the native valve (panel f of figure 3). Moreover calcification deposits were shown within the native tissue (figure 3 panel e), marked with dark brown stain and the patch was completely inert.

Figure 1: Panel A - A4C view - shows the colour flow regurgitant jet of the right atrioventricular valve. Panel B - A4C view - shows the dense signal and blunt triangular shape of the CW signal. They represent echocardiographic pictures of severe insufficiency of right atrioventricular valve.

Figure 2: a) Anterior view of native heart removed at transplantation without the atrial chambers, with the epicardial fibrous tissue reaction; b) posterolateral view of the right atrial cavity showing the huge dilatation of the coronary sinus. The AV septal defect has been repaired with a double patch which became calcific (black arrows); c) transverse section showing the moderate hypertrophic thickening of the parietal wall of both ventricles and the rettilinization of the interventricular septum d) Ex vivo X-Ray of the heart showing the position of valves prosthesis and the tricuspid valve calcifications (white arrows).

Figure 3: SIS-ECM patch used for the TV valve reconstruction. a) macroscopic view of the a-v junction, opened along the acute margin with a complete view of the tricuspid valve, the dotted line marks the SIS-ECM patch at the septal leaflet of the reconstructed tricuspid valve; b) H&E staining (12x of magnification) of the septal leaflet with the SIS-ECM surrounded by fibrous tissue reaction. Note the oval hole (asterisk) where the surgical stitches have been removed for histological inclusion; c) Azan-Mallory staining specific for fibrosis (12x od magnification); d) Elastic fibers van Gison, in black the elastic fibers, in red the fibrous tissue (12x of magnification); e, f) von Kossa staining specific for calcium, in black the calcium peripheral tissue of SIS-ECM patch, no evidence of calcium deposits within the patch, (12x and 25x of magnification); f) CD45 staining showing the inflammatory cells infiltration surrounding the SIS-ECM patch (50x of magnification).

Comment

Traditional repair material for cardiac tissue (eg, bovine pericardium) is known to have the main disadvantages of having no growth potential, and of degenerating with calcification and thickening [8]. The SIS-ECM is a decellularized, non-cross-linked, treated biological material which was designed to be immunologically inert and biologically adaptive. The bioscaffold characteristics were designed to enable native cells to infiltrate the SIS-ECM. Specifically, such material when used for heart valve repair was designed to function immediately after implantation as a competent heart valve and to perform efficiently at lower transvalvular pressure gradients as experienced by the normal tricuspid valve. Previous reports have shown that when SIS-ECM is integrated within the patient's own living tissue, with little or absent "foreign body" reaction may function well for some time [4].

To confirm this hypothesis, we investigated the biological reaction and remodeling of SIS ECM in the right AV valve reconstructed leaflet after 8 years for implantation. We hypothesized that SIS ECM could maintain a durable architecture and remodel to resemble surrounding tissues, with infiltration of native host cells.

However, our histology results do not corroborate previous encouraging reported results. We observed a lack of complete SIS ECM reabsorption, extensive fibrosis reaction and scarring. In fact, inflammation and calcifications were not detected in the SIS-ECM leaflet. Inflammation was extensive and persistent in the native component of the recostracted valve, in relation to stickers required to anchor the SIS-ECM flap to the valve. Also calcifications were confirmed to the native tissue.

In conclusion, the SIS-ECM patch failed to remodel in a structured and anatomical fashion. Progressive mechanical and remodeling failure might be explained by the complexity of the cardiac structures and the host's chronic inflammatory response, leading to fibrosis and calcification.

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