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Pathological Changes of Adult Mitral Valves after Failed CorMatrix ECM Repair

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Abstract

Background and objectives: CorMatrix acts as a tissue scaffold and is intended to promote the proliferation of small vessels and tissue remodeling to replicate normal tissue function.

Methods: At Temple University Hospital, Philadelphia, PA, USA from 2013 to 2016, CorMatrix material was utilized during mitral valve anterior leaflet augmentation repair in 25 adult patients, and four patients required repeat interventions at 4–12 months (8.25 ± 4.35 months) after the initial repair. This study evaluated the pathological changes in four patients.

Results: Histological examination of the CorMatrix showed matrix degradation in all cases. At 4 months after repair, mixed acute and chronic inflammatory cells that included eosinophils were visible within the matrix, which was more severe around the suture material. Later, the extent of inflammation abated and became more chronic with macrophage dominance. Some macrophages and multinucleated cells were visible deep in the matrix. The neovascularization was limited to the tissue–matrix boundary at early time points; the more mature vessels with dilated lumens extended deeper into the matrix as time increased, combined with some elongated fibroblast-like cells. In addition, marked acute and chronic inflammation with neutrophil and eosinophil infiltrate was identified in the surrounding native tissue at 4 months, especially around the suture material. Marked granulomatous inflammation was identified in all cases, with prominent multinucleated giant cells present at later time points (50%). Immunohistochemical staining for CD68 and CD163 showed prominent M2 macrophages in the CorMatrix and surrounding tissue.

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Author contributions

Study concept and design (HW), acquisition of data (BC, HW), analysis and interpretation of data (BC, HW), drafting of the manuscript (BC), critical revision of the manuscript for important intellectual content (BC, HW)

Conflict of interest

One of the authors, Dr. He Wang has been an editorial board member of *Journal of Clinical and Translational Pathology* since May 2021.

Data sharing statement

No additional data are available.

Conclusions: Our results demonstrated time-dependent changes in failed CorMatrix repaired valves after mitral valve repair, with macrophages and neovascularization in the matrix 12 months after the initial repair.

Keywords

CorMatrix; Mitral valve repair; Graft failure; Inflammation

Introduction

Reconstruction or augmentation of the mitral valve is a common cardiac surgical procedure, which frequently requires additional biological or prosthetic tissue to act as an anatomical substitute.[1,2] Traditionally, autologous or cross-linked xenopericardium has been used for anterior leaflet augmentation (ALA).[3] However, these materials are particularly susceptible to fibrosis, thickening, calcification, and retraction over time.[4,5] Recently CorMatrix extracellular matrix (ECM) (CorMatrix Cardiovascular, Alpharetta, GA, USA), which is manufactured from porcine intestinal submucosa, has emerged as a leading choice for several cardiovascular and peripheral vascular repair procedures, especially in pediatric populations.[6–10]

CorMatrix ECM is a biological scaffold, 90% of CorMatrix ECM is collagen (predominantly type I), other components include proteoglycan, fibronectin, laminin, thrombospondins, osteopontin, tenascins, and growth factors.[11] In theory, the three-dimensional structure of CorMatrix supports the ingrowth of host cells; it is sufficiently bioactive to initiate and maintain molecular control over proliferation and differentiation of the host cells and is absorbable.[12] In addition, CorMatrix ECM is decellularized to reduce antigenicity, and therefore, reduce the inflammatory response.[13] Preliminary experimental findings revealed that CorMatrix ECM does not promote a strong inflammatory response and is calcification resistant.[5] Early clinical studies found that CorMatrix was suitable for mitral valve repair, with excellent valvular function postoperatively.[14–16] In 2005, CorMatrix ECM was approved by the Food and Drug Administration (FDA) for cardiovascular and peripheral vascular repair. However, more recent data, especially from clinical studies with larger subject numbers, suggested a significant number of re-operations after CorMatrix ECM repair.[10,17,18] In contrast to successful arterial reconstruction,[19,20] histological examination of the tissues that were collected during the valve re-operation revealed intense chronic inflammation, a lack of significant resorption of the implanted material, and little or no remodeling into a structure that resembled native valve tissue, in contrast to the manufacturer's claims.[2,21] This inconclusive clinical data requires careful histological examination. Most reported studies have been conducted in pediatric populations, the repaired site varied from valve to septa to artery, and the procedures in one study were usually conducted by different surgeons.[2,9,21]

In this study, the histological findings from a mitral leaflet removed following CorMatrix placement for ALA of mitral valves in adult patients at a single institution are presented. All procedures were conducted by one experienced vascular surgeon. Our data

indicated significant chronic inflammation, the proliferation of small vessels and capillaries (neovascularization), and a few fibroblast-like cells in these CorMatrix ECM.

Methods and materials

This study was a hospital-based retrospective case study where patient's charts were reviewed and pathological analysis was performed on previously collected tissue. CorMatrix was utilized during mitral valve repair surgery for patients who were admitted to Temple University Hospital (Philadelphia, PA, USA) with severe mitral regurgitation. The use of CorMatrix ECM for mitral leaflet patches was FDA approved for cardiac tissue repair. The Institutional Review Board of Temple University Hospital (Philadelphia, PA, USA) approved the exemption of this study.

The study group constituted patients with Carpentier type IIIa or IIIb mitral valve disease and severe mitral regurgitation that were admitted from 2013 to 2016. The surgeries were performed at Temple University Hospital (Philadelphia, PA, USA) by a single vascular surgeon. Median sternotomy or a minimally invasive approach that utilized the da Vinci Si surgical robotic system (Intuitive Surgical, Sunnyvale, CA, USA) was used as the surgical approach. Despite the approach, the same surgical technique was used for all of the valve repairs. The only exceptions were in cases of rheumatic valves, where a commissurotomy was often added. Gore-Tex sutures were used to place the patch in robotic repairs and Prolene sutures were used in open repairs. Cardiopulmonary bypass with the cardioplegic arrest was used in all cases. The left atrium was entered, and the valve was inspected. An annuloplasty band sizer (Medtronic Simulus, Minneapolis, Minnesota, USA) based on inter-trigonal distance was used to size the anterior mitral leaflet. An incision was then performed at the base of the anterior leaflet that extended from beyond the left commissure to beyond the right commissure, which nearly detached the anterior leaflet and lay passively on the posterior leaflet. Any restrictive secondary chords were resected. The same sizer was then used as a cookie-cutter type of template to fashion the ECM patch by placing it on the graft and outlining it with a marker. The patch was placed into the defect in the anterior leaflet and sewn into place. After the patch was secured, a flexible Medtronic Similus (Minneapolis, Minnesota, USA) annuloplasty band was sutured into place with Proline in either a running or interrupted suture line. The valve was tested with normal saline for competence. The atrium was closed, and the patient weaned off the bypass circuit. Immediate postoperative transesophageal echo was performed to assess valve function.

The only indication for re-operation was the presence of severe recurrent mitral regurgitation associated with graft failure. Graft failure was defined as patients that had evidence of severe mitral regurgitation on follow-up echocardiography regardless of symptoms. Native valve tissue and graft sections were submitted for histologic examination.

Native valve tissue and graft explanted at surgery were fixed in 10% neutral buffered formalin, embedded in paraffin, and the long axes of all tissue pieces were 5 μm. The sections were stained with Hematoxylin and Eosin (H&E), Masson's Trichrome, and Miller's Elastic stain as previously described.[21] Immunohistochemistry was performed on paraffin-embedded sections of explanted CorMatrix, and the surrounding tissue was

prepared using standard methods.[21] Immunohistochemistry was performed. CD 68 was used as the marker for macrophages, CD 163 for M2 macrophages, and CD 138 for plasma cells. Native valve tissue and explanted grafts were evaluated for degree and type of inflammation, fibrosis, eosinophil response, foreign body giant cell reaction, calcification (confirmed by Alizarin red stain), and neovascularization of the surrounding native tissue on a semi-quantitative basis (none; mild = grade 1; moderate = grade 2; marked = grade 3) by two pathologists. The inflammation was scored as follows: grade 0, if no inflammatory cells were present; grade 1, if there were occasional scattered cells or one group of ≥20 cells; grade 2, if there were several groups of ≥20 cells; and grade 3, if there were many groups of ≥20 cells or one group of ≥100 cells.[22] Acute inflammation was defined as an inflammatory infiltrate that contained any number of neutrophils. Chronic inflammation was defined as an inflammatory infiltrate that consisted of small lymphocytes, plasma cells, and macrophages. The presence or absence of degeneration (myxoid changes and breakdown of the collagenous background) of CorMatrix material and adjacent tissue fibrosis was assessed and confirmed by Masson's trichrome stain. Constructive remodeling of CorMatrix, which was defined by the replacement of CorMatrix by native cardiac cells and organized viable collagen, was evaluated.

Statistical analysis

All *p*-values were calculated using Fisher's exact test. Statistical data is expressed as mean ± SD or mean ± SE. Statistical significance is expressed as $*P < 0.05$, $**P < 0.01$ ($P > 0.05$ usually does not need to be denoted). GraphPad Prism 5.0 (GraphPad, La Jolla, CA) software was used for all statistical analyses.

Results

During 2011–2014, 25 patients underwent anterior mitral leaflet (AML) augmentation with porcine intestinal ECM. The study group was composed of four patients with severe mitral regurgitation who were re-operated on. The only indication for re-operation was the presence of severe recurrent mitral regurgitation associated with graft failure. Native valve tissue and graft sections were submitted for histologic examination. The time from an initial mitral valve repair to graft failure was from 4 to12 months (8.25 ± 4.35 months). The remaining 21 patients had an uneventful clinical course to date. The demographic data, which included the types of mitral valve regurgitation, were not different between functional and dysfunctional CorMatrix valve groups (Table 1).

The pathological changes were divided into two locations: CorMatrix and the surrounding native mitral valve tissue. Suture material that demarcated the boundary between native valve tissue and CorMatrix material was identified in all four mitral valve specimens. The explanted CorMatrix were relatively loose with areas that demonstrated r evidence of degradation at <5 months (Fig. 1); the matrix became more solid >9 months; however, areas of degradation were still visible. At earlier time points, mixed acute and chronic inflammatory cells, which included eosinophils were visible, which was more severe around the suture material and at the boundary between the matrix and native tissue, with some macrophages and highly immature capillaries and scant macrophages (Fig. 2); at later time

points, the extent of the inflammation abated, and became more chronic, with macrophage dominance. Some macrophages and multinucleated cells were visible deep in the matrix. No significant eosinophils were identified. The neovascularization was limited to the native tissue–matrix boundary at 4 months, the more mature vessels with dilated lumens extend deeper into the matrix at 12 months, together with some elongated fibroblast-like cells (Fig. 3). No calcification was identified at any time points. The histological features did not differ in the patient with a previous history of rheumatic fever. The cause of mitral regurgitation was CorMatrix failure and evidence of endocarditis was not noted in any case (Table 2).

The valve tissue around CorMatrix showed moderate to marked lymphoplasmacytic and neutrophil infiltration, especially around the suture material, with prominent eosinophils. Marked granulomatous inflammation tissue was identified in all cases, with prominent multinucleated giant cells at later time points (50%) (Fig. 4). No significant neutrophils or eosinophils were observed at later time points (Table 3).

Trichrome and Elastin stains were performed on all the slides, which revealed focal areas of fibroblastic proliferation and neovascularization, respectively. Elastic staining showed the elastic fibers in the native mitral valves. Immunohistochemical staining for CD 68, CD 138, and CD 163 was performed on all the cases. CD 68 and CD 163 were used as markers for total and M2 macrophages, respectively and all of the cases demonstrated infiltration of the valve tissue with macrophages, especially M2 type macrophages (4/4, 100%) (Figs. 5 and 6). CD 138 highlighted the plasma cells and were focally positive in 2 out of 4 (50%) of cases. Therefore, the results showed a mixed inflammatory infiltration of M1 and M2 macrophages that was consistent with pro- and anti-inflammatory responses. Despite the time range of the clinical follow-up, no significant differences were noted in the inflammatory patterns.

Discussions

In this group of adult patients, a proportion (28%) of patients with mitral valve ALA with CorMatrix needed re-operation. Histological examination showed a range of pathological changes in the matrix, from matrix degradation to acute inflammation to chronic inflammation to neovascularization from 4 to 12 months after mitral valve repair. With (approximately 12 months), more mature neovessels and some fibroblast-like cells were identified deep in the matrix. However, even in the longest follow-up case, no remodeling into tissue similar to the three-layered native mitral valve was identified in the mitral valve of failed CorMatrix repairs. A significant number of eosinophils were observed in all cases at early time points, surrounding the tissue and in the matrix, which suggested a hypersensitivity reaction to the implanted CorMatrix in human tissue at early time points. However, the eosinophils largely disappeared in the matrix at later time points (at 12 months). These data were different from previous reports[21] in pediatric patients with some interesting observations and highlighted the time-dependent pathological changes in adult patients, especially within implanted CorMatrix.

Tissue substitutes are required in the repair and reconstruction of cardiac valves. However, the ideal material is unknown.[23] Autologous pericardium (with or without glutaraldehyde

fixation) and cross-linked xenopericardium have been traditionally used for patch repairs, but they are susceptible to fibrosis, thickening, calcification, and retraction and cannot facilitate tissue growth.[5,24,25] Homografts of valves have been used for many years, but their long-term success is age-dependent and a reliable supply is not always available.[26] Various prosthetic materials (*e.g.*, polyethylene terephthalate [Dacron, DuPont, Wilmington, DE] and polytetrafluoroethylene [Gore-Tex, W. L. Gore & Associates, Flagstaff, Ariz]) are usually rigid and increase reactive inflammation and endocarditis.[27] CorMatrix, a largely acellular non-cross-linked ECM bioscaffold, is a relatively new choice in the constructive tissue remodeling of heart valves. Two important features of CorMatrix are: (1) biocompatibility, which should not promote intense inflammation or infection; and (2) could potentially undergo remodeling and regeneration. The mechanisms by which CorMatrix undergoes remodeling are not understood. One theory is the bioinduction model of remodeling: (1) degradation of the non-native matrix by circulating enzymes or early infiltrating cells, or both particularly M2-type macrophages; (2) release of growth factors during scaffold degradation, which includes vascular endothelial growth factors and transforming growth factor; (3) growth factors from the scaffold induce host cell infiltration, which includes circulating bone marrow-derived cells, such as endothelial and mesenchymal progenitor cells; and (4) sustained tissue formation and neovascularization.[28–31] Animal studies and initial clinical studies appear to support the previous hypothesis that ECM is an inert, ideal biological scaffold.[14–16,32,33]

Recent studies indicated the presence of moderate to severe inflammation, at least in a subpopulation of valve repairs, which contradicted the initial theory that ECM is biologically inert. Zaidi *et al.*[2] studied the histopathological changes in grafts in CorMatrix in nine patients with mitral valve prolapse for a maximum follow-up period of 9 months. Their findings of the intense inflammatory response included macrophages and giant cells in contact with the material, surrounded by lymphocytes, macrophages, plasma cells, and eosinophils. Rosario-Quinones *et al.*[17] studied six patients with congenital cardiac disease who had a re-operation after the implantation of CorMatrix patches. They found dense, eosinophilic inflammatory tissue infiltrates, granulation tissue, and fibrosis on explanted specimens. Rosario-Quinones *et al.* attributed the intense eosinophilia present in their explants to a hypersensitivity reaction, to α-gal epitopes (Galalpha1–3Galbeta1-(3)4GlcNAc-R) present in the porcine material. Woo *et al.*[21] observed chronic inflammation in 11 out of 12 explanted CorMatrix heart valves and acute inflammation in 3 cases. Woo *et al.* noted that acute inflammation was present only in cases of short follow-up. In addition, they observed that CorMatrix was not resorbed in any case and remodeling was not associated with organized collagen, which agreed with the findings in this study. Two case reports found calcifications within the CorMatrx, a feature that was reported in the autologous pericardium and not in the CorMatrix.[5,34] However, previous histological reports were mainly in pediatric patients, the subject numbers were small, and the results were from different cardiac repair procedures. In this study, all tissues originated from the same mitral valve augmentation procedures and all surgical procedures were conducted by one surgeon. The underlying cause for all mitral valve regurgitation cases was hypertension. Our current study design allowed the observation of time-dependent changes in CorMatrix in a relatively homogenous study group. This study confirmed the previous

results in animal models, which illustrated the early degradation and inflammation inside the matrix, and later angiogenesis and a few fibroblast-like cells in the matrix. However, even with the longest follow-up, no remodeling into tissue similar to the three-layered native mitral valve was identified in the mitral valves of failed CorMatrix repair. In addition, pathologic changes were identified and reported in previous human pediatric populations.[21] Significant numbers of eosinophils were observed in all cases at early time points, in the surrounding tissue and in the matrix, which suggested a hypersensitivity reaction to the implanted CorMatrix in humans. Marked granulomatous inflammation tissue was identified in all cases, with prominent multinucleated giant cells at later time points (50%). Another important observation in this study was that the lymphoplasmacytic inflammation was more prominent around the suture material at all time points, which suggested that the Prolene suture was partly responsible for triggering the inflammation and foreign body reaction.[35] The results from this study suggested that some foreign body reactions occurred in adult patients after CorMatrix mitral valve augmentation; however, the level was not higher than that induced by the Prolene suture. More importantly, infiltrating cells, particularly M2-type macrophages and neoangiogenesis occurred in the CorMatrix after implantation, even after a failed repair.

In this study, none of the implanted CorMatrix was remodeled into tissue similar to the three-layered native mitral valve. This was in contrast to the case report by Stelly *et al*.[36] that revealed that 5 years after grafting, CorMatrix remodeled into viable, fully cellularized, vascularized, non-fibrotic connective tissue that was similar to the native pericardium. Gerdisch *et al*.[14] described that CorMatrix bioscaffold was a satisfactory material for mitral valve regurgitation in a variety of surgical situations, which included endocarditis.[14] However, a thorough histological examination was not conducted in this study. Our study indicated that some elements of remodeling occurred in the implanted CorMatrix, which included macrophage infiltration and neovascularization. However, our study design did not confirm the CorMatrix could eventually be remodeled into a three-layered native mitral valve or structures that were functionally similar to native valves at later time points. This could be determined from the careful examination of tissue samples from failed CorMatrix implantation procedures and functionally successful repair procedures. The number of successful procedures, in this study, was in the majority (72%).

This study has several limitations. The sample size was small and based on a single institution. Therefore, the data might not be representative of the entire population. In addition, more long-term follow-up should be conducted to strengthen determine the favorable remodeling that might occur later during implantation.

Conclusions

Our results demonstrated time-dependent changes in CorMatrix after mitral valve augmentation repair, with macrophages, angiogenesis, and a few fibroblast-like cells in the matrix 4–12 months after initial repair. However, no remodeling into tissue similar to the three-layered native mitral valve was identified in the valves of failed CorMatrix repair. Because the majority of the repair procedures in this and several other published studies were successful without recurrent regurgitation,[10] pathological examination and comparison

of clinically successful and failed CorMatrix repaired valves is required to fully evaluate the body's reaction to CorMatrix cardiac repair.

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Abbreviations:

ALA	anterior leaflet augmentation
ECM	extracellular matrix
FDA	Food and Drug Administration
H&E	Hematoxylin and Eosin

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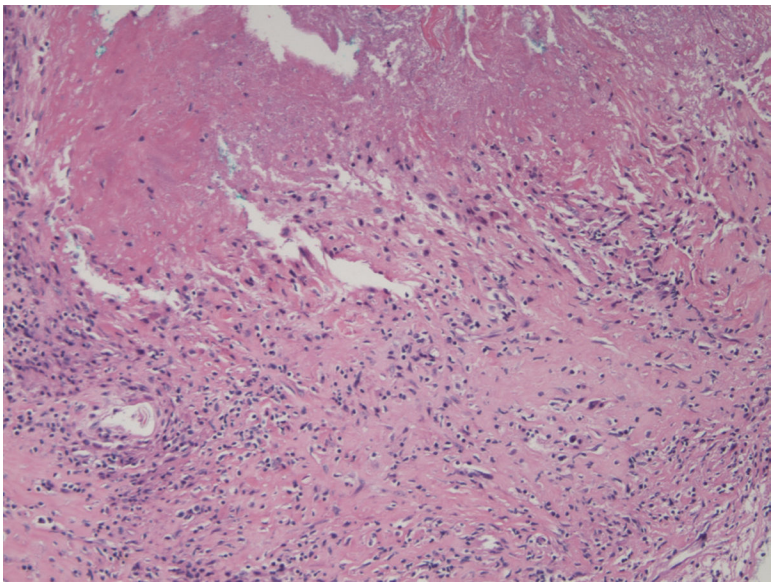

Fig. 1. Degenerative CorMatrix and inflammation.

CorMatrix material 1 month after implantation shows extensive matrix degradation, together with acute and chronic inflammation (H&E staining ×100).

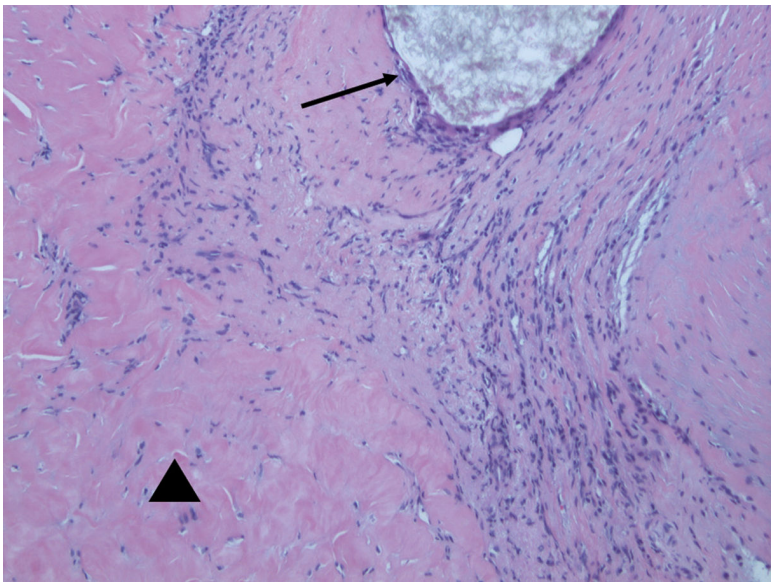

Fig. 2. Inflammation around the Prolene suture.

Ten months after implantation, chronic inflammation and neovascularization were much more significant around the suture (arrow) compared with the surrounding CorMatrix material (triangle, H&E staining ×400).

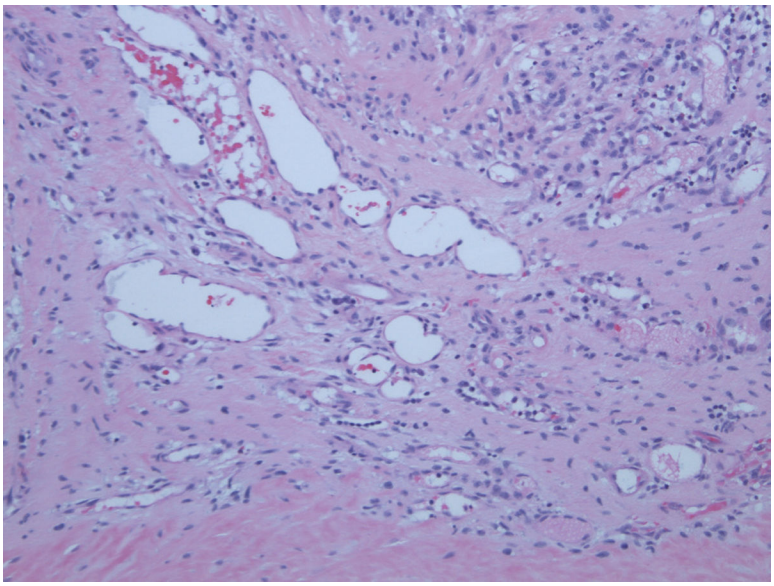

Fig. 3. Focal neovascularization into the CorMatrix.

Twelve months after implantation, larger, dilated vessels were visible deep into the CorMatrix, together with mild chronic inflammatory cells (H&E staining ×400).

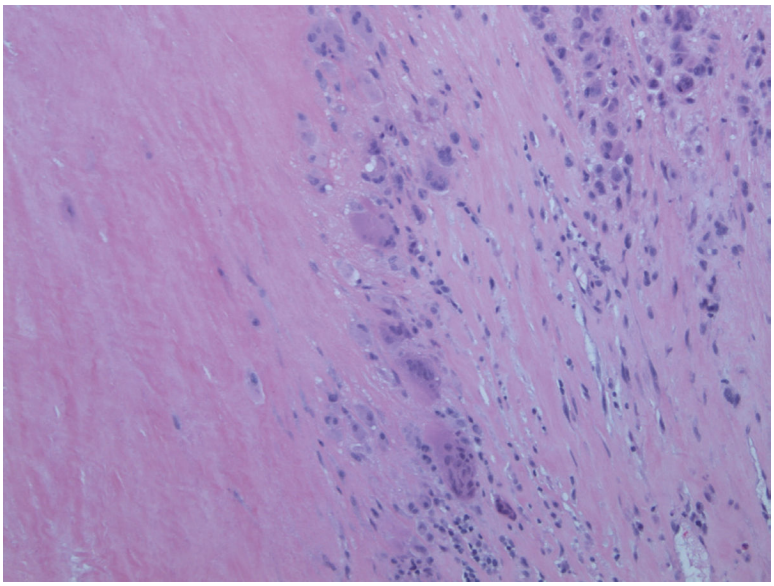

Fig. 4. Granulomatous inflammation around CorMatrix.

Granulomatous inflammation with a significant number of multinucleated giant cells was characteristic 4 months after implantation (H&E staining ×400).

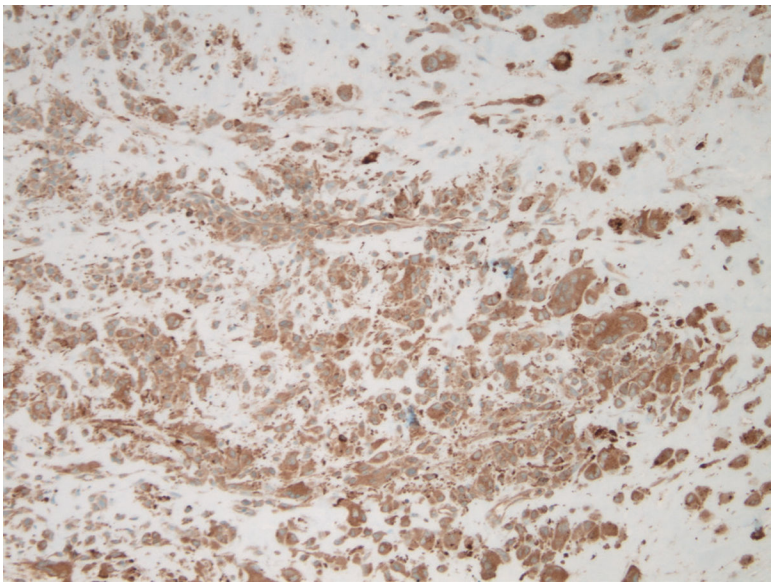

Fig. 5. Immunohistochemical stain of CD 68.

Twelve months after implantation, the majority of infiltrating cells into CorMatrix were CD 68 positive, revealing their macrophage nature including a few multinucleated giant cells (×200).

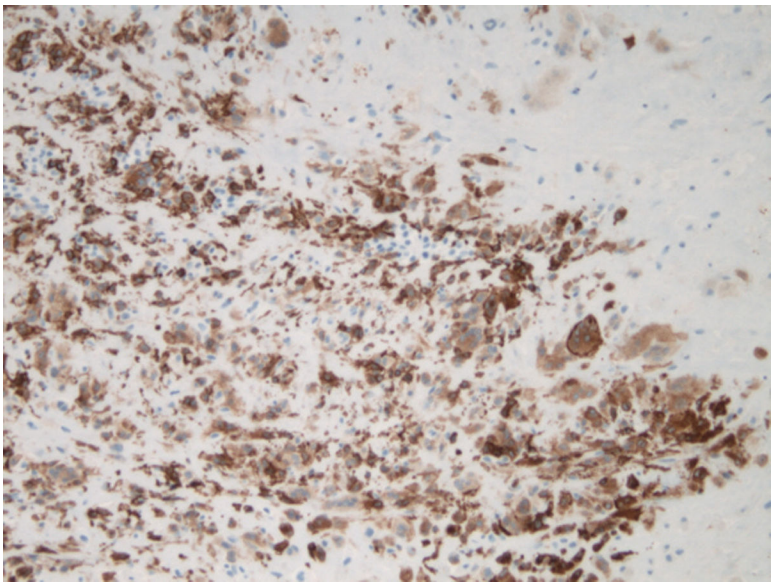

Fig. 6. Immunohistochemical stain of CD 163.

Twelve months after implantation, a large portion of infiltrating macrophages into CorMatrix were CD 163 positive, including a few multinucleated giant cells (×200).

Table 1.

Basic characteristics of patients

	No Dysfunction	Dysfunction	*p*-value
Age (years, mean ± SD)	63.3 ± 10.8	62.0 ± 13.3	0.83
Body mass index (kg/m^2, mean ± SD)	33.2 ± 6.5	27.9 ± 5.9	0.14
LVEF (%, mean ± SD)	48.4 ± 14.1	50.7 ± 13.4	0.77
Gender, n (%)			>0.99
Male	7 (33.3)	1 (25.0)	
Female	14 (66.7)	3 (75.0)	
Autoimmune disease, n (%)	4 (19.0)	1 (25.0)	>0.99
Diabetes, n(%)	3 (14.3)	1 (25.0)	0.53
COPD, n (%)	3 (14.3)	1 (25.0)	0.53
Hypertension, n (%)	17 (81.0)	4 (100.0)	>0.99
Type of MR, n (%)			>0.99
Type IIIa	14 (66.7)	3 (75.0)	
Type IIIb	7 (33.3)	1 (25.0)	

Note: Continuous variables are expressed as means ± SD. COPD, chronic obstructive pulmonary disease; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation.

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Table 2.:

Histopathologic characteristics of CorMatrix

	Patient 1	Patient 2	Patient 3	Patient 4
Time *in situ* (months)	12	12	5	4
Chronic inflammation	3	2	1	1
Acute inflammation	1	0	2	2
Angiogenesis	1	1	0	1
Mesenchymal cells	1	1	2	1
Calcification	0	0	0	0
Eosinophils	0	0	1	1
3D layer of valve	0	0	0	0

Note: the parameters were graded in the CorMatrix material. Grading parameters were as follows: grade 0 = none; grade 1 = mild; grade 2 = moderate; and grade 3 = marked (as discussed in methodology). Presence of degeneration was evaluated within CorMatrix material. Presence of native vessel formation within CorMatrix material was evaluated.

Table 3.:

Histopathologic characteristics of surrounding tissue

	Patient 1	Patient 2	Patient 3	Patient 4
Time graft *in situ* (months)	12	12	5	4
Chronic inflammation	3	2	2	2
Acute inflammation	2	0	3	3
Angiogenesis	2	1	0	3
Mesenchymal cells	1	1	2	1
Calcification	0	0	0	0
Granulomatous inflammation with giant cells	3	2	0	0

Note: the parameters were graded in the native tissue adjacent to CorMatrix material. Grading parameters were as follows: grade 0 = none; grade 1 = mild; grade 2 = moderate; and grade 3 = marked (as discussed in methodology).