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LONG-TERM COMPLICATIONS EVIDENCED STUDYING THE EXPLANTED *GORE® HELEX®* ATRIAL SEPTAL DEFECT OCCLUDER SEVEN YEARS AFTER IMPLANTATION: A CASE REPORT

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ABSTRACT

We present the results of the first morphological study of a Gore® HELEX® Septal Occluder 30 mm that was explanted seven years after interventional implantation due to a significant left-to-right shunt (7 mm) which resulted from the stretching of the concomitant patent foramen ovale by the occluder after atrial septal defect closure. Complete endothelialization of the surface of the device, the formation of the connective tissue around the implant, minor chronic inflammation, the appearance of foreign body giant cells and weakened myocardial cells adjacent to the implant as well as enhanced expression of matrix metalloproteinases were demonstrated.

Keywords: *Atrial septal defect; Gore® HELEX® septal occlude; matrix metalloproteinases, myocardium*

INTRODUCTION

Percutaneous transcatheter closure of secundum atrial septal defects (ASDs) is an efficient and safe method in long-term with high procedural success rates.

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Long-term complications are very rare which increases the importance of reporting them.

The Gore® HELEX® occluder is composed of a single piece of nickel-titanium (nitinol) wire with a patch of expanded polytetrafluoroethylene (ePTFE) attached along its length. The elastic property of nitinol is used to form the wire frame into two opposing disks that bridge and close the septal defect. The ePTFE is specially designed to facilitate rapid cell penetration, thereby promoting rapid tissue ingrowth, resulting in permanent defect closure and device stability [7]. Endothelial, interstitial and inflammatory cells that are located at the biomaterial interface can release various tissue mediators, remodel, and, even, degrade the tissue increasingly expressing matrix metalloproteinases (MMPs) [2]. MMPs often contribute to cardiovascular remodeling, and enhanced MMP expression is related to the variety of pathological processes and diseases, including aneurysm formation, atherosclerosis, myocardial infarction, hypertension, and cardiomyopathies [3].

MATERIALS AND METHODS

Light microscopy

After surgical explantation, the device was dissected and fixed in 10% buffered formalin. For light microscopy, the parts of the device containing only ePTFE without nitinol wire were dehydrated in a series of graded ethanols and embedded in paraffin. Histological sections were stained routinely with hematoxylin and eosin (H&E) and Masson's trichrome. For immunohistochemistry, we used a panel of four anti-MMP antibodies: mouse monoclonal anti-MMP-2 (Novocastra, Newcastle, UK, Leica Biosystems, clone 17B11, 1:40), anti-MMP-9 (Novocastra, Newcastle, UK, Leica Biosystems, clone 15W2, 1:40), anti-MMP-10 (Novocastra, Newcastle, UK, Leica Biosystems, clone 5E4, 1:25), and rabbit polyclonal anti-MMP-3 (Biorbyt, Cambridge, UK, Biorbyt Ltd., 1:300) antibody; mouse monoclonal anti-CD34 (Cell Marque, Rocklin, CA, USA, clone QBEnd/10, 1:100), anti-CD68 (DacoCytomation, Glostrup, Denmark, clone PG-M1, 1:50), and anti-α-smooth muscle actin (SMA) (DacoCytomation, Glostrup, Denmark, clone 1A4, 1:100) antibodies. The antigen sites were visualized with 3,3'-diaminobenzidine (DAB) substrate kit (Cell Marque, Rocklin, CA, USA). The sections were counterstained with Mayer's hematoxylin. The expression of antigens was estimated at ×100 up to ×400 magnification, using Leica light microscope (LEICA, LEITZ DMRB, Germany).

Electron microscopy

The explanted device and the adjacent tissue interface were studied by a scanning electron microscopy. The small part of the ePTFE patch and the adjacent cardiac tissue was fixed in 2.5% glutaraldehyde, postfixed in 1% OsO_4, dehydrated, dried by the critical point method using liquid CO_2, mounted onto metal stub, covered with gold using an automated sputter coater (JFC-1300, JEOL, Japan). Finally, samples were examined under a JSM-6490LV scanning electron microscope (JEOL, Japan) at accelerating voltage of 10kV using SEI mode and magnification ×1000-×4000.

CASE REPORT

In December 2007, a 33-year-old female patient presented with complaints of fatigue, breathlessness on exertion and palpitations, and was admitted to Pauls Stradins Clinical University Hospital. Transesophageal echocardiography (TEE) revealed 8 mm large Ostium Secundum ASD. Additionally, a small patent foramen ovale (PFO) was also detected. The patient underwent a TEE-guided transcatheter closure of ASD with stretched diameter of 15 mm using the Gore® HELEX® Septal Occluder 30 mm. The final position of the device and its configuration was stable but suboptimal with partial flaring of the disks and non-significant residual leak above the implant. After consulting with device providers a decision was made to follow-up the patient. Aspirin 100 mg per day was started and continued for six months.

There were no significant shunt and the change of the device position revealed in one month transthoracic echocardiography examination. The patient was asymptomatic and was lost of follow-up for six years until presented in January 2014 with exertional dyspnea, dizziness, and fatigue for six months. By TEE a significant left-to-right shunt of 7 mm through the PFO resulting from the stretching of the PFO by the device was revealed. The device was explanted, and a surgical closure of interatrial communication by primary suture closure was performed. Postoperative echocardiography confirmed immediate complete closure of ASD.

RESULTS

Gross pathology

By gross examination, the Gore® HELEX® Septal Occluder appeared to be completely covered by a smooth whitish layer of tissue revealing thorough endothelialization. The nitinol frame of the device was covered only by a thin layer of tissue and remained visible through it. The wire appeared macroscopically intact and without ruptures. No thrombi or vegetations were found adjacent to the device.

Light microscopy, immunohistochemistry and electron microscopy

By histological examination, no fibrin deposits or evidence of acute inflammation were detected. Following recommendations, published previously [4], the following regions of the specimen were distinguished: the outer cellular layer of the neoendothelium, pseudointimal connective tissue inserted between the neoendothelium and the device, and the neotissue represented by the connective tissue between the disks of the occluder. We found complete endothelialization of the luminal surface of the device, consisting of a single layer of CD34-positive endothelial cells. In turn pseudointima was identified composing of the dense connective tissue, sparse capillaries and few spindle-shaped fibroblast-like cells oriented parallel to the neoendothelium. These cells were α-SMA-positive. Interestingly, because of the microporous structure of ePTFE, we observed deep tissue ingrowth inside the patch itself. By contrast, to pseudointima, the neotissue consisted of the loose connective tissue with well-developed vascularization and abundant chaotically oriented fibroblast-like cells that stained positive for α-SMA. Importantly, along with the inner surface of the ePTFE patch, we found numerous multinucleated CD68-positive foreign body giant cells arranged in a single row at the cardiac tissue-device material interface (Fig. 1). Additionally, minor lymphocytic and plasmacytic infiltration was observed within the loose connective tissue in regions of marked angiogenesis.

Studying possible long-term effects of insufficiently functioning occluder, and its associated foreign body reaction as well as remodelling of cardiac tissue by the estimation of MMPs we found marked expression of MMP-9 by endothelium, foreign body giant cells, macrophages, fibroblasts-like cells and cardiomyocytes (Fig. 2), whereas the expression of MMP-2, 3 and 10 was almost nil. Additionally, we observed extracellular MMP-9 related immunostaining in the dense connective tissue of the pseudointima revealing uniformly stained

collagen fibers. Interestingly, that the loose connective tissue of the neotissue did not stain immunopositive for MMP-9 when compared to the pseudointima.

We noted that the atrial myocardium located near the device showed marked morphological alteration, particular cardiomyocyte hypertrophy, the enlargement of nuclei and cytoplasmic myofilament destruction. These changes were accompanied by fibrotic tissue ingrowth into the myocardium (Fig. 3).

The myocardium obtained for the ultrastructural studies consisted of differently shaped and sized muscle cells which slightly bifurcated and connected

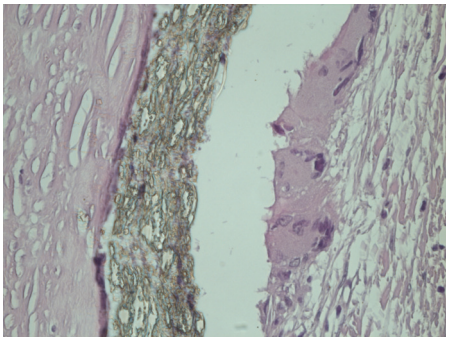

Figure 1. Foreign body giant cells arranged in a single row at the surface of the occluder, H&E, ×400.

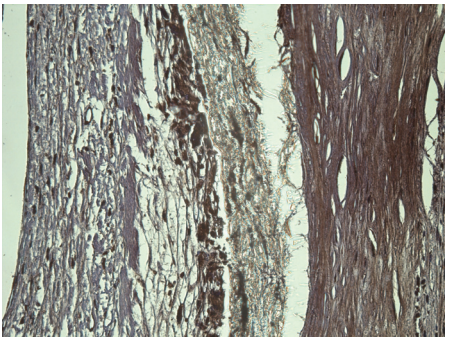

Figure 2. Marked expression of MMP-9 by endothelium, foreign body giant cells, macrophages, and fibroblast-like cells. Pseudointimal collagen fibers appear to be densely packed and uniformly stained, ×250.

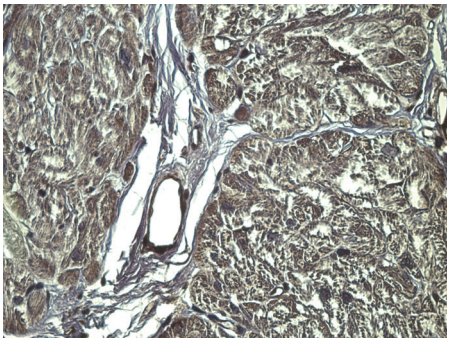

Figure 3. Cardiomyocytes exhibiting MMP-9 immunopositivity. Fibrotic changes of the myocardium, distortion of cardiomyocytes, nuclear polymorphism and partial myofilament destruction were demonstrated, ×400.

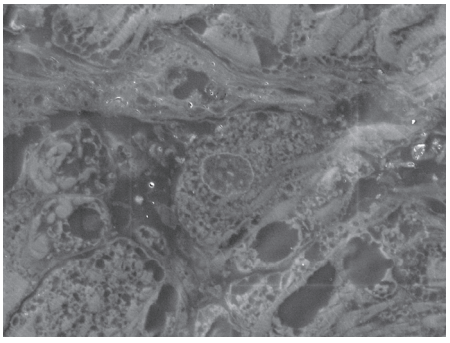

Figure 4. Scanning electron microscopy revealing a region of myocardium demonstrating haphazardly oriented, differently shaped and sized cardiomyocytes. The content of cytoplasm includes microfilamnets, mitochondria, and the endoplasmic reticulum, ×2000.

with neighbouring cells, mostly at the ends of cellular trunks. The cytoplasm of cardiomyocytes revealed a varying number of microfilaments, differently sized and oriented mitochondria, and tubules of the endoplasmic reticulum (Fig. 4). Some cardiomyocytes showed loosening of the cytoplasmic content.

DISCUSSION

Over the past decade, the interventional closure of amenable ASD has become the treatment of choice in most centers worldwide. However, very limited data deciphering histopathological changes and some aspects of biocompatibility of ASD closure devices in humans is currently available [5]. Some of these studies were performed on explanted the Amplatzer® Atrial Septal Defect Occluder that was the first occlusion device to obtain approval for commercialization. To date, only two devices have been approved by the US FDA with an indication for the transcatheter closure of ASD: the Amplatzer® Atrial Septal Defect Occluder (December 2001) and the Gore® HELEX® Atrial Septal Defect Occluder (August 2006) [5].

In contrast to the former, to our knowledge, there are no morphological studies on explanted Gore® HELEX® atrial septal defect occluder in humans, except for the only one study performed on dogs [7].

The major drawback of the previous histopathological studies is that these studies were conducted investigating a short period of implantation set between three months and two years after device implantation. Since the implanted devices are expected to function lifelong, it could be too little time to assess local tissue response and biocompatibility. In our case, the device was explanted seven years after implantation.

As was described in the previous reports of the Amplatzer® Atrial Septal Defect Occluder, we found foreign body giant cells located at the tissue-material interface – a convincing evidence of a chronically persisting inflammatory response [1,4,5,6]. It is supposed that foreign body giant cells can release various tissue remodeling mediators and lead to the degradation of several biomaterials with subsequent device failure [2]. Additionally, lymphocytic and plasmacytic infiltration was also observed. Whether this ongoing inflammatory reaction, directed against the implanted device, could result in device dysfunction or impact on its safety is unknown. To date, there are no reported adverse short-term and long-term effects of foreign body immune reaction to nitinol wire and ePTFE patch.

Biomaterial adherent macrophages can secrete a variety of proteins that modulate fibrosis and form a fibrous capsule around the device [2]. To study possible effects of giant cells on cardiac tissue and extracellular matrix (ECM) remodeling, we performed immunohistochemical analysis of the explanted device using antibodies to MMPs, CD34, CD68, and SMA. We found marked extracellular and cytoplasmic expression of MMP-9 in vascular endothelium, foreign body giant cells, macrophages, fibroblasts-like cells and cardiomyocytes. It is worth noting that the levels of MMPs expression were greatly varying. The expression of MMP-2, 3 and 10 was almost nil, whereas the levels of MMP-9 expression were high. Collagen fibers were stained immunopositive in the outer dense connective tissue layer (pseudointima) but no expression was found in the inner loose connective tissue layer (neotissue). The higher degree of ECM remodeling in the pseudointima may subsequently lead to the excessive encapsulation of the device.

The most striking finding was a morphological heterogeneity and the distortion of cardiomyocytes, and loosening of the cytoplasmic organelles including microfilaments. Additionally, fibrotic changes in the myocardium were also noted. Whether these alterations in the myocardium are the results of the enhanced MMP-9 expression and foreign body immune reaction or hemodynamic characteristics attributable to the significant left-to-right shunt over PFO, is a matter of debate. It was described previously, that enhanced MMPs expression could be associated with the variety of cardiovascular diseases, including aneurysm formation, atherosclerosis, myocardial infarction, hypertension, and cardiomyopathies. However, these pathological processes were described for MMP-2 [3]. In our study, we found only the MMP-9 expression, which together with MMP-2 constitute the same group of gelatinases. According to our results, MMP-9 might have a significant role in maintaining chronic inflammatory response with the foreign body reaction and promoting fibrous encapsulation of the implanted device.

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