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Anastomotic Intimal Hyperplasia after Prosthetic Arterial Bypass

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ABSTRACT

Objectives: This study evaluated the inflammatory response to the presence of implanted synthetic vascular grafts, during the three chronological phases of the encapsulation process: early, organisation, and late.
Methods: We examined a number of 66 synthetic grafts of which 59 were polyethylenterephtalat (47 Terom and 12 Dacron), and 7 were ePTFE. The mean implantation time was 31.5 weeks (range 1 day to 9 years.
Results: In the organisation phase (during 2 weeks and six months after implantation), we had 26 grafts. In the Polyethylenterephtalat prostheses (Terom, Dacron), the thickness of the external capsule in our specimens was 0.5-1.8 mm; a granulation tissues rich in young cells starts penetrating the prostheses interstitials, and leads to a tissue that contains a markedly increased number of foreign body giant cells. The Polytetrafluoroethylene (ePTFE) prostheses have a thin external capsule with a limited, focal giant cell reaction, and the interstitials are occupied by young hypocellular granulation tissue and type I collagen; there is a thin internal capsule without foreign-body reaction and endothelial cells originating in the native artery endothelium; near the anastomoses. In the late phase (after six months post-implantation), we had 29 grafts. The Polyethylenterephtalat prostheses had an external capsule with a thickness ranging between 0.8 and 2.5 mm; the prostheses interstitials contains a fine fibrous connective tissue with macrophages and multinucleated giant cells that penetrate from the internal and external capsule; the internal capsule has mesenchyme proliferation; the foreign-body giant cells are also. The ePTFE prostheses have a thin, fibrous, external capsule with small areas displaying multinucleated giant cells, and a very thin one or two-layer cell internal capsule with rare foreign-body reaction.
Conclusion: The study demonstrates the intense inflammatory reaction (multinucleated giant cells in the internal and external capsules) one-month post-implantation, and also a persistent chronic inflammatory reaction (foreign body granulomas in both capsules and the surrounding tissue) at over 1 year post-implantation, in the polyethylenterephtalat prostheses; these changes were not found in the ePTFE prostheses, which leads us to the conclusion that the implanted synthetic vascular grafts cause a foreign-body reaction dependent on the material used.

Keywords: prostheses, intimal hyperplasia, forein body reaction.

1. Introduction

Improvements in surgical technique and development of synthetic vascular grafts allow us to perform the reconstruction of arteries. Although most bypass procedures with synthetic grafts have good early results, they may later fail. An important factor of late graft failure is the development of intimal hyperplasia, mainly in synthetic grafts. On the contrary, artery grafts are less affected (ex. internal mammary artery). It is therefore very important to improve the performance of synthetic grafts making it as successful as autologus arterial grafts. Control of the formation of intimal hyperplasia in synthetic grafts is hereby crucial. After implantation, the synthetic arterial prostheses become encapsulated; the surrounding tissue reaction to Teflon or polyethylenterephtalat is similar to the inflammatory reaction to aseptic, inert foreign bodies. There are three chronological phases to the encapsulation process: early, organization and late.

2. Materials and Methods

In order to analyze the encapsulation process of the synthetic arterial prostheses, a high-pressure system, we examined 66 prostheses or segments of prostheses; 61 were removed during reinterventions for thromboses and five postmortem. There were two types of prostheses in our study: 59 were polyethylenterephtalat knitted prostheses, (47 Terom - a Romanian original prostheses and 12 Dacron - Bard Medical from Medtronic) and seven expanded polytetrafluoroethylene prostheses (ePTFE, Gore-Tex). The mean implantation time was 31.5 weeks (range one day to nine years).

After the prostheses were cut longitudinally, fragments from the anastomotic and central areas were obtained for macroscopic and microscopic examination; they were prepared according to the standard protocol for optical microscope, using hematoxylin-eosin and Trichrom-Masson. We elected not to use any special coloring techniques for the endothelial cells. All the specimens were examined by an experienced pathologist using optical and polarized light microscopy.

An informed consent was obtained from the patients, and the study was approved by the institutional ethics committee on human research. The authors have no affiliation or financial support with the pharmaceutical industry, nor any conflicts of interest to disclose.

3. Results

3.1 The "early" phase

Considering that in the early encapsulation process the host versus graft reaction is trivial, we focused on the changes occurring after the first two weeks after implantation.

3.2 Organization phase

This phase begins after the first two weeks and ends in six months; the changes that occur during this phase are simi-

lar to the normal inflammatory process: monocytes, lymphocytes, fibroblasts and macrophages are dominant, accompanied by rare foreign body giant cells and new capillaries formation. Twenty-six prostheses were in this stage.

3.2.1 Polyethylenterephtalat prostheses (Terom, Dacron)
The external capsule. In two to three weeks, a granulation tissues rich in young cells starts penetrating the prostheses interstitials. This process ends in three to four weeks and leads to a tissue tightly adherent to the prostheses that contains a markedly increased number of foreign body giant cells. Some of these cell display phagocytosis of small synthetic particles. Other cells seen are increased number of fibroblasts and macrophages that also penetrate the prostheses interstitials. The thickness of the external capsule in our specimens was 0.5-1.8 mm and its cellular proliferation is much more pronounced than the internal capsule.

Prostheses interstitials. Thin filaments of connective tissues can be found in the prostheses interstitials, especially in its external layer. Monocytes and macrophages from both the internal and external connective tissue penetrate the interstitials (photo 1). The internal capsule macrophages originate in the blood circulating through the prostheses and are most commonly seen around neocapillaries. They have increased phagocytosis around the prosthetic material with subsequent transformation into foreign body giant cells. The neocapillaries continue to proliferate having a tendency to merging and dilation. Also at this level, the internal and the external capsules send extensions that merge in the middle and form the intercapsular or transprosthetic bridges.

The internal capsule. This part is thin, discontinuous, and has areas covered by fibrin alternating with bare areas. It has an increased number of round cells, lymphocytes, plasmocytes, and small macrophages. The lack of complete endothelization is the main substrate for thrombosis. The endothelization process starts at the prostheses margins where the native arterial endothelium extends covering the luminal prosthetic surface. Occasionally, some prostheses displayed endothelial cell that are not uniformly and continually organized.

3.2.2 Polytetrafluoroethylene (ePTFE) prostheses
The external capsule. In comparison to the polyethylenterephtalat prostheses, ePTFE prostheses with the same implantation time have a thin external capsule with a limited, focal giant cell reaction.

Prostheses interstitials. The interstitials are occupied by young hypocellular granulation tissue and type I collagen.

The internal capsule. There is a thin internal capsule without foreign-body reaction and endothelial cells originating in the native artery endothelium. Near the anastomoses, it has increased thickness and rare giant cells neighboring the prostheses (photo 2).

3.3 The "late" phase
This stage begins after six months post-implant; the mesenchyme is rich in fibers and hypocellular and occasionally the protein structure is lost. The mesenchyme proliferation, somewhat limited, can be found in the internal capsule. Twenty-nine prostheses were in this stage.

3.3.1 Polyethylenterephtalat prostheses (Terom, Dacron)
The external capsule. The thickness of the external capsule in our specimens was 0.8-2.5 mm; it contains mature connective tissue, rich in cells and neocapillaries located in the immediate vicinity of the prostheses. Inside the dense connective tissue rich in fibrils, located in the prostheses transition zone, an almost perfect circle of monocytes, macrophages, and foreign-body giant cells is found. Foreign-body reaction is present in all the examined prostheses with the multinucleated foreign-body giant cells arranged around the synthetic fibers. Some areas display fragmentation and phagocytosis of the synthetic fibers by the multinucleated giant cells (photo 3).

Prostheses interstitials. These areas contain a fine fibrous connective tissue with macrophages and multinucleated giant cells that penetrate from the internal and external capsule and are attached to the synthetic particles. During the long period of encapsulation, the synthetic particles continue to be degraded. Occasionally, the phagocytosis can be inferred from the loss of regular pattern in the synthetic fibers. The interstitials are crossed by intercapsular bridges containing neocapillaries and multinucleated foreign-body giant cells (photo 4).

The internal capsule. In this phase the capsules are completely organized with a minimal activity still occurring in the internal capsule. The internal capsule has mesenchyme proliferation that includes monocytes, macrophages, capillaries and blood vessels. The foreign-body giant cells are also present and occasionally the monocytes and macrophages form a line in the transition zone to the prostheses. In some Terom prostheses, the foreign-body reaction leads to foreign-body granulomas surrounding the synthetic fibers (photo 5). In these area, the internal capsule thickness is markedly increased, especially at the distal anastomoses sites, up to levels of 2.0-3.5 mm (average 2.6mm) versus other areas with lesser degrees of foreign-body reaction (average 1.2mm). Only 30% of the prostheses have a uniform layer of endothelial cells on the luminal surface and only on a 1.5cm length near the distal anastomoses. The remaining of the internal or luminal surface has only sporadic endothelial cells.

3.3.2 Polytetrafluoroethylene (ePTFE) prostheses
The external capsule. The ePTFE prostheses have a thin, fibrous, external capsule with small areas displaying multinucleated giant cells (photo 6). Teflon prostheses external capsule has cavities filled with prosthetic material, massive numbers of macrophages and multinucleated giant cells crossing the entire thickness of the prostheses. These form real "highways" that are perpendicularly oriented on the prosthetic ring-like structures.

The internal capsule. There is a very thin one or two-layer cell internal capsule with rare foreign-body reaction. Near the distal anastomoses, the thickness reaches 1.0mm and there are giant cells neighboring the prostheses. The endothelial cells are only present near the anastomoses and are not organized into an uniform layer (photo 7).

4. Discussions
Earlier studies hypothesized that the prostheses encapsulation process is similar to the foreign body encapsulation process, consisting in undifferentiated cells originating in the surrounding tissue and the circulating blood. More recent theories offer an alternate model for the process. Florey [1] describes for the first time in 1962 the presence of neointimal orifices of 120 microns diameter located at the anastomosis level. In 1986, Clowes [2] identifies the so called "endothelial channels" that open on the endothelial surface through small orifices. These channels are transprosthetic neocapillaries as shown in experimental studies involving micro-corrosive molding and were documented only in the areas where endothelization was present. Because these channels are absent in ePTFE prostheses that have decreased porosity, the authors concluded they are the main source for a complete and uniform endothelization.

Kogel et al [3] showed the presence of endothelial channels in four human prostheses, and Zhang et al [4] also agree that native artery vasa vasorum plays an important role in the endothelization process. All prior studies agree that unlike the animal model, the endothelization in humans is very slow and never completes. Why does this happen? One possible answer is that synthetic material, especially

polyethylenterephtalat prostheses, inhibit somehow the encapsulation.

Clowes et al [2] and Greisler et al [5] demonstrated that Dacron prostheses have a different encapsulation process than ePTFE and hypothesized that this was due to several factors:

- the existence of large structural differences in the polymers used to woven the prostheses leading to different degrees of peri-graft inflammation with the release of different inflammatory products in the surrounding tissues;
- Dacron prostheses allow less transparietal capillary formation compared to ePTFE;
- the internal surface of Dacron prostheses have larger quantities of In111 radioactively marked thrombocytes versus the ePTFE, potentially inhibiting endothelization;
- the Dacron prostheses also attract polymorphonuclear leukocytes and can activate both the classic and alternate complement pathways more than ePTFE; activating polymorphonuclear leukocytes has been shown to inhibit endothelization
- macrophages activation accompanied by TGF-beta release is also more pronounced in Dacron prostheses.

Cavallaro et al [6] demonstrated in an experimental study that the Dacron threads led to an early, intense inflammatory reaction, with inflammatory cells penetrating the prostheses and leading to a chronic inflammation. Polypropylene and ePTFE threads lead to mild to moderate inflammatory reactions. Using another experimental model, Zippel et al [7] found the presence of a chronic inflammatory reaction associated with thromboses inside Dacron prostheses, suggesting that Dacron prostheses led to an unfavorable host response.

Our study demonstrates, in the polyethylenterephtalat prostheses, the existence of an intense inflammatory reaction characterized by the presence of multinucleated giant cells in the internal and external capsules one month post-implantation and also by a persistent chronic inflammatory reaction with foreign-body granulomas in both capsules and the surrounding tissue at over one year post-implantation. These changes were not found in the ePTFE prostheses in our study [8], and also are not described in the previously published literature. Camileri [9] and Xue et al [10] identified giant cells in the external capsule of one ePTFE prosthesis obtained 18 months post-implantation.

There are several consequences of a chronic inflammatory reaction that should be considered: inhibited transparietal neocapillaries formation, inhibited vasa vasorum growth in the prostheses wall, neointimal hyperplasia, and lack of endothelization. Thickening of the intimal layer and external capsule in the polyethylenterephtalat prostheses lead to increased prostheses wall rigidity after implantation.

5. Conclusions

Implanted synthetic vascular prostheses cause a foreign-body reaction dependent on the material used. In the polyethylenterephtalat prostheses there are giant multinucleated cells in the external capsule, interstitials, and internal capsule, in the anastomotic areas (especially distal) seen even in prostheses implanted for more than 9 years. In ePTFE prostheses, the giant cells are only found in the external capsule. In the distal anastomotic areas of the polyethylenterephtalat prostheses, where foreign-body granulomas are present, the neointima has a markedly increased thickness compared to the areas with decreased foreign-body reaction.

Figure legends

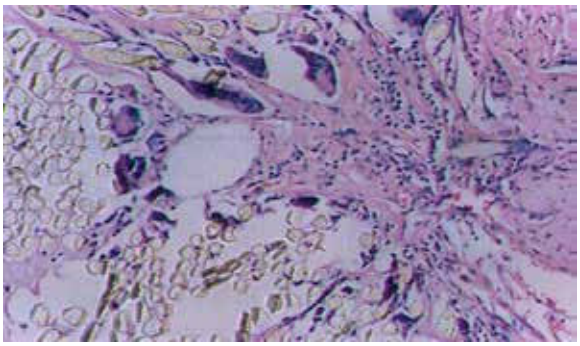

photo 1Terom prostheses – II-nd phase, 15 weeks after implantation. Giant cells marked with arrow. (magnification x200) Col. H-E x200

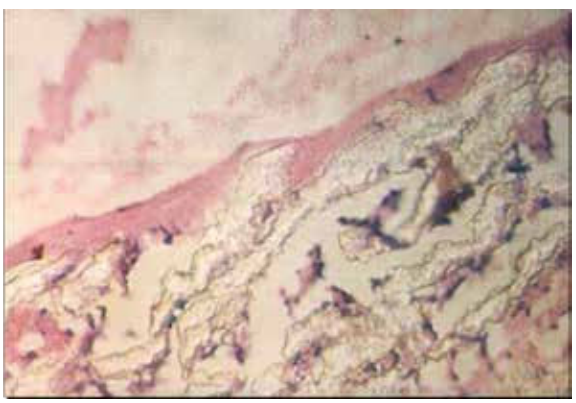

photo 2 ePTFE prostheses, II-nd phase, 7 weeks after implantation. Endothelial cells at the distal anastomoses (arrow). (magnification x400) Col. H-E x400

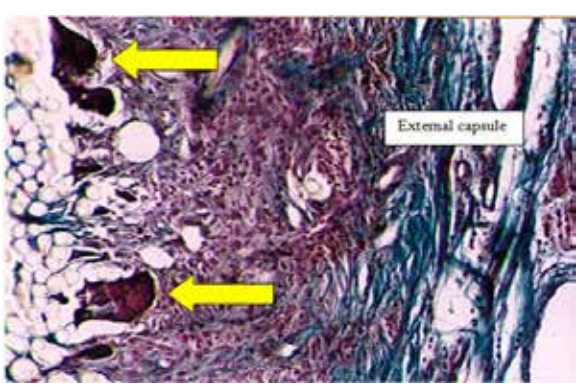

photo 3 Terom prostheses – III-rd phase, 24 mounth after implantation. Giant cells reaction arround the prosthetic graft (arrow).(magnification x200) Col. Tricrom Masson x200

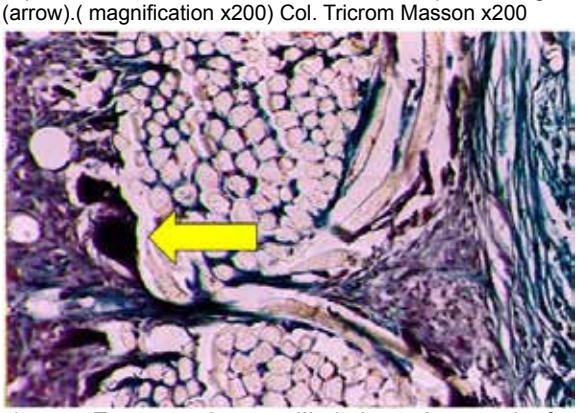

photo 4 Terom prostheses – III-rd phase, 24 mounth after

implantation. Giant cell (arrow). (magnification x200) Col. Tricrom Masson x200

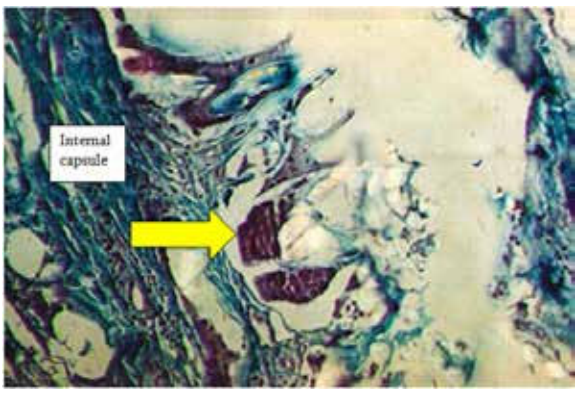

Photo 5 Terom prostheses – III-rd phase, 36 mounth after implantation. Giant cells (arrow).(magnification x200) Col. Tricrom Masson x200

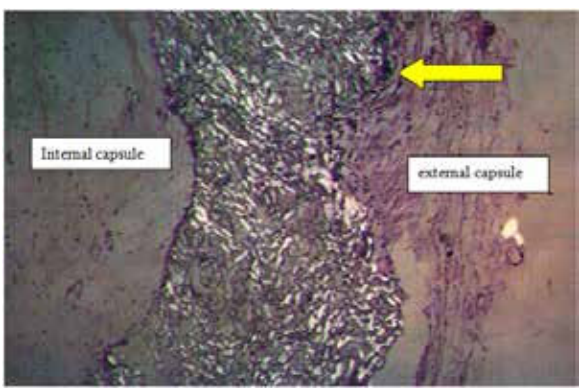

Photo 6 ePTFE prostheses - III-rd phase, 8 mounth after implantation. Giant cells in the external capsule of the prostheses.(magnification x40) Col. H-E x40

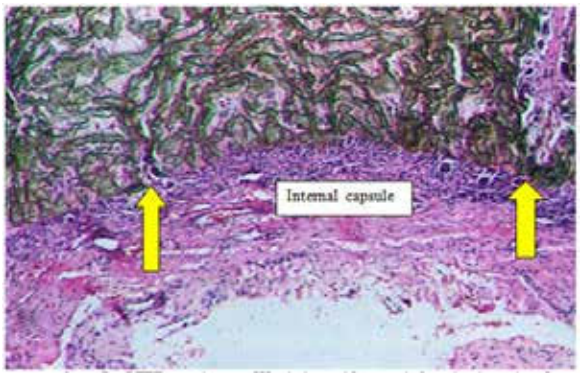

photo 7 ePTFE prostheses - III-rd phase, 18 mounth after implantation. Internal capsule, at the distal anastomoses. Low giant cell reaction.(magnification x40) Col. H-E x40

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