Chronic Granulomatous Inflammation after CyPass[®] Implantation

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Established Facts

- Polyimide material is described as having excellent in vivo biocompatibility.
- No prolonged inflammation was described after CyPass[®] implantation in several studies.
- The reason for CyPass[®] withdrawal in August 2018 was a marked endothelial cell loss 5 years following its implantation.

Novel Insights

- Persisting clinical inflammation in association with an intense foreign body reaction is described 19 months after CyPass[®] implantation.
- Previous multiple glaucoma surgeries could have been discussed as a contraindication prior to CyPass[®] Micro-Stent implantation.
- Histopathological evaluation of explanted stents provides better insight into possible therapy failure and should therefore be performed routinely.

Keywords

Immunohistochemistry · Glaucoma implant · Foreign body granuloma · Minimally invasive glaucoma surgery

Abstract

A 65-year-old patient suffering from pseudoexfoliation glaucoma and multiple previous surgeries at the right eye underwent CyPass[®] explantation 19 months after CyPass[®] Micro-Stent implantation due to chronic inflammation in the anterior chamber. Histologically, a foreign body granuloma around and in the CyPass[®] implant was found. We conclude that patients with previous multiple glaucoma surgeries should not undergo CyPass[®] Micro-Stent implantation.

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Introduction

The CyPass[®] Micro-Stent is an implant for minimally invasive glaucoma surgery with rare adverse effects that were described in several studies from 2014 to 2016. Its market withdrawal was announced in August 2018 due to a marked endothelial cell loss after a follow-up of 5 years [1].

Case Report/Case Presentation

A 65-year-old woman has been suffering from pseudoexfoliation glaucoma since 2007 with slight glaucoma damage to her right eye. Multiple (glaucoma) surgeries were performed within the period of May 2014 to February 2015 (i.e., selective laser trabeculo-

Fig. 1. OD CyPass® implant in the anterior chamber at 4 o'clock (arrow).

Fig. 2. HE overview. Tube-shaped yellow stent material with a central oblong opening and plenty of lateral openings.

plasty, trabeculotomy, phacoemulsification with IOL implantation, and CyPass® Micro-Stent implantation with postoperative topical steroid therapy for several weeks) (Fig. 1). The CyPass® Micro-Stent is a 6.35 mm long stent used in minimally invasive glaucoma surgery with 64 fenestrations made of polyimide. Its insertion into the suprachoroidal space through a clear cornea incision enables suprachoroidal outflow of aqueous humor to lower the intraocular pressure.

Nevertheless, in the case of our patient trabeculectomy and cyclophotocoagulation became necessary later due to further uncontrolled glaucoma with recurrent intraocular pressure peaks reaching 50 mmHg. Additionally, 12 months following the stent implantation a chronic inflammation of the anterior chamber occurred. The differential diagnosis of (viral) uveitis was ruled out by a negative anterior chamber sample for HSV-1, HSV-2, CMV, VZV, EBV, and rubella virus. The visual acuity was 0.4 OD, also due to postoperative macular edema, and 1.0 OS. Finally, 19 months after CyPass® implantation its explantation was performed since this was the most likely reason for the chronic inflammation accompanied by the recurrent intraocular pressure rise.

With HE staining, a tube-shaped yellow plastic material with a central oblong opening and plenty lateral openings was visible under the microscope (Fig. 2). The surface of the oblong foreign body was covered by a flat layer of connective tissue (Fig. 3). With PAS staining, no PEX material could be found (Fig. 4). All of the lumens and microholes of the stent were filled with and surrounded by fibrous scar tissue with Vimentin-positive fibrocytes accompanied by a granulomatous inflammation consisting of numerous CD68-positive macrophages and multinucleated giant cells (Fig. 5). Immunohistochemical staining against CD3 showed several positively stained T lymphocytes (Fig. 6) and the staining against HSV was negative. Some cells were S100 and Melan A positive, most probably representing melanocytes, which might have migrated from the adjacent iris entering the area of the CyPass® Micro-Stent.

The histopathological diagnosis was foreign body granuloma around and in the CyPass® implant.

After the stent explantation 3 more cyclophotocoagulations were performed within the following 6 months, until 1 year later a Descemet membrane endothelial keratoplasty (DMEK) was necessary after the development of bullous keratopathy due to endothelial cell failure. Endothelial cells were not countable anymore and completely missing in the histopathological examination of the removed Descemet membrane. Finally, nearly 3 years after stent explantation, the patient developed a beginning phthisis bulbi at the right eye.

Discussion/Conclusion

In 2 German studies CyPass® stent implantation was performed in combination with cataract surgery [2, 3]. In the study from 2014, five out of 136 study eyes suffered from postoperative inflammation lasting longer than 1 month, which might also have been caused by cataract surgery. Further adverse effects were hypotonia (15.4%) and stent obstruction likely caused by overgrowing iris tissue (8.8%). In the study of 2016 including 167 study eyes, no prolonged inflammation was described. García-Feijoo et al. [4] performed solely CyPass® implantation in 65 study eyes and did not observe any inflammatory reaction either initially or 1 year later in 55 patients. Partial obstruction of the stent was observed in 3.1% of the cases. Vold et al. [5] are the only ones who listed pseudoexfoliation as an exclusion criterion and described iritis

Fig. 3. HE detail. Flat layer of connective tissue covering the surface of the oblong foreign body.

Fig. 4. No PEX material could be found in the PAS stain.

only as a transient adverse event resolving after the application of topical steroids in 8.6% of the patients who received a combination of cataract surgery with CyPass[®] implantation out of 374 study eyes. In 2.1% of cases, stent obstruction occurred due to focal peripheral anterior synechia [5]. Sirova et al. [6] stated an initially excellent in vivo biocompatibility of polyimide used in the CyPass[®] Micro-Stent after subcutaneous implantation of a hydrogel-coated polyimide membrane in mice. Nevertheless, 4 and 9 weeks later giant cell granulomas formed around the membrane as seen in our case. Foreign body reactions have also been described in polyimide-based intraneural implants [7].

In general, granulomatous inflammations describe a group of subacute and chronic inflammations of different etiologies that occur after infections, foreign body reactions, hypersensitivity reactions, and others [8]. A simple granuloma is defined by a circumscribed accumulation of macrophages and T lymphocytes [9]. The cause of the formation of a granuloma can usually be identified via isolation of the pathogen. The formation of a foreign body granuloma seems dependent on the characteristics of the foreign body but also on endogenous factors. It can occur in almost any organ and its development continues over weeks [8, 10]. CD68-positive macrophages which are also referred to as histiocytes are recruited through several im-

Fig. 5. Numerous CD68-positive macrophages (red) around and in the CyPass® Micro-Stent also forming multinucleated giant cells (*) in the pore surrounded by fibrous scar tissue (**). The arrow points towards the inside of the stent.

Color version available online

Fig. 6. Immunohistochemical staining against CD3. The arrow indicates several positively stained T lymphocytes.

Color version available online

mune signals to further build epithelioid cells or fuse into polynuclear giant cells most likely via $\text{TNF-}\alpha$, $\text{INF-}\gamma$, and IL-4 [8]. Together they form the foreign body granuloma which may also contain fibroblast proliferation and usually lacks T lymphocytes in or around the granuloma [8, 9].

To our knowledge, no foreign body reaction following minimal invasive glaucoma surgery has yet been described in the literature, either after CyPass® Micro-Stent implantation or after any other implant (iStent®, Hydrus™, XEN®, or InnFocus MicroShunt®) [11]. Two of those implants, i.e., the iStent®, which consists of heparin-coated nonferromagnetic titanium, and the Hydrus™, made of nitinol (nickel-titanium alloy), are metal based. The medical-grade titanium is described as biocompatible with the eyes, with no foreign body reaction after iStent® implan-

tation [12]. Titanium is widely used in bone surgery or dental implants, whereas titanium is no longer seen as “inert” but induces a foreign body reaction that allows osseointegration of the foreign body as a healing process – its long term result is seen as dependent on a “foreign body equilibrium” [13]. For nitinol, which is used in the Hydrus™, there is also no description of prolonged inflammation or foreign body reaction in the eyes, whereas the usage in a coronary stent has induced a minimal foreign-body reaction in rabbits [14–16]. In the 2-year results after implantation of XEN®, an ab interno gelatin stent, 2 out of 218 eyes showed iritis, which was not further described [17]. Interestingly, 41.1% of the eyes underwent needling but no material surrounding the implant was histologically analyzed [17]. When it was invented, the gelatin was

described as biocompatible and as an established material for many medical applications causing no foreign body reaction in the eyes [18]. In contrast, after subcutaneous implantation in mice a strong foreign body reaction to glutaraldehyde-crosslinked gelatin hydrogels could be shown [19]. The InnFocus MicroShunt® consists of the polymer SIBS (polystyrene-block-isobutylene-block-styrene), which was specifically developed to control a foreign body reaction [20]. It was successfully used as coating material of a metallic coronary stent with no biodegradation and only minimal tissue reaction [21]. When used in the eye as an InnFocus MicroShunt® it was shown to be “ultrastable with virtually no foreign body reaction in the body, which manifests as clinically insignificant inflammation and capsule formation in the eye” [22]. Until now no foreign body granuloma has been described with this device. In general it can be stated that although the above mentioned materials are described as biocompatible with no known foreign body reaction in the eyes, building a foreign body granuloma should be considered after implantation of any foreign material.

In summary, only minimal inflammation following CyPass® Micro-Stent implantation alone or in combination with cataract surgery in eyes without known prior surgeries has been described. The persisting intraocular inflammation of our case in association with an intense foreign body reaction might be attributed to previous multiple glaucoma surgeries and/or pseudoexfoliation. Thus, previous multiple glaucoma surgeries and/or pseudoexfoliation might be considered as potential contraindications for (intra)ocular implantation of polyimide. In addition, our case shows that histopathological evaluation of explanted stents provides a better insight into a possible therapy failure and should therefore be performed routinely.

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Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient gave written informed consent for publication of this case, including publication of images.

Disclosure Statement

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Author Contributions

All of the authors were involved in acquisition, analysis, or interpretation of the data for this work, drafted this work or critically revised it for important intellectual content, gave final approval of the final version of this work, and agree to be accountable for all aspects of this work in ensuring that questions related to the accuracy or integrity of any part of this work are appropriately investigated and resolved.

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