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CORRESPONDENCE

Recurrent In-Stent Restenosis in a Symptomatic Nonatherosclerotic M1 Plaque

Successful Treatment with Paclitaxel-Eluting Balloon Dilatation after Repeated Failure of Conventional Balloon Reangioplasty

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Introduction

Intracranial arterial stenosis is a frequent cause of major stroke [1]. Medical treatment with either platelet antiaggregation or anticoagulation may be an option for asymptomatic patients and for those not suitable for endovascular therapy. In patients with high-grade symptomatic stenoses, balloon dilatation using coronary stents [2], neurovascular variants thereof [3], or self-expanding stents [4] offers better protection from stroke. In dedicated centers, these procedures are carried out safely and efficiently. The long-term course, however, remains a concern. The dilemma is that drug-eluting stents (DES) provide good long-term results, but are just too stiff for elongated vessels. For all bare-metal stents (BMS), no matter if balloon-expandable, self-expanding, stainless steel, cobalt-chromium or nickel-titanium, in-stent restenosis (ISR) rates of 30% and higher have been reported.

Since ISR of > 50% lumen loss may again cause cerebral ischemia, treatment of these patients is mandatory. In the past, conventional balloon dilatation or the deployment of a second stent was established clinical practice. Some years ago, Scheller et al. could show in pigs that a short-term exposure of the vessel wall to the antiproliferative drug paclitaxel is able to inhibit vascular smooth muscle cell proliferation for several days [5]. Angioplasty of coronary ISR performed with iopromide- and paclitaxel-coated balloons (drug-eluting balloon [DEB]) prevents restenosis more frequently and longer than the use of bare-surface balloons [6].

We report the clinical history of a young patient with a symptomatic, presumably inflammatory proximal middle cerebral artery (MCA) plaque, which was treated by balloon dilatation and self-expanding stent deployment, followed by recurrent intracranial ISR. Three retreatments with conventional balloons were again followed by severe intimal hyperplasia. After angioplasty with a DEB, no further ISR occurred.

Case Report

An otherwise healthy 19-year-old woman presented with recurrent transient ischemic attacks. Medical history was free from any cerebrovascular risk factors or known heart disease. Neurological signs and symptoms included episodes of right hemiparesis and aphasia. Diffusion-weighted magnetic resonance imaging (DWI-MRI) showed several foci of restricted diffusion in the left MCA supply territory. Digital subtraction angiography (DSA) on April 17, 2008, revealed a high-grade stenosis in the proximal segment of the left M1 segment with residual flow (Fig. 1a). Endovascular treatment with stent percutaneous transluminal angioplasty (PTA) was planned for the next day and the patient received the standard dual platelet antiaggregation loading with 500 mg acetylsalicylic acid (ASA) and 600 mg

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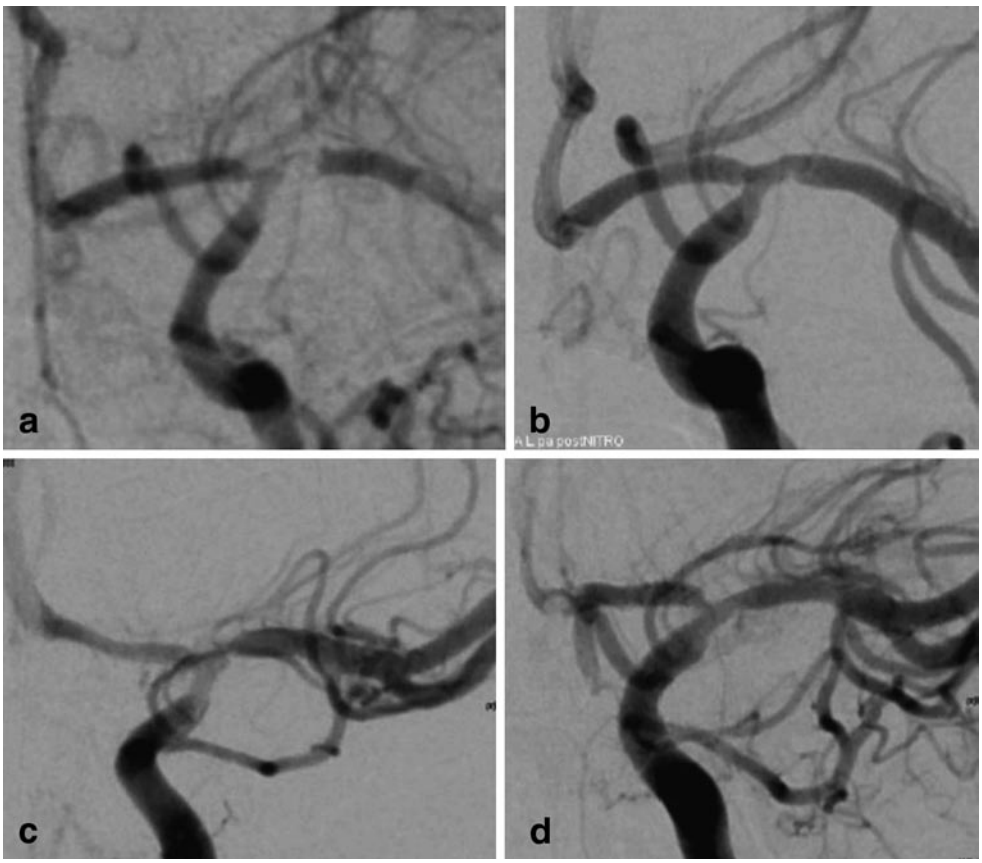

Fig. 1 Initial thrombus narrowing the left M1 segment (**a**). One day later under systemic heparinization and dual platelet inhibition, the thrombus was resolved and a long plaque extending from the distal ICA to the proximal MCA became visible (**b**). Despite continued medication, DSA 3 days later again showed a critical vessel narrowing (**c**). Conventional balloon dilatation and deployment of an Enterprise stent restored the vessel diameter with some degree of residual stenosis of the distal ICA and the M1 segment (**d**). The plaque itself remained visible. There was a preexisting high-grade stenosis of the proximal A1 segment, which remained untreated since the left ACA was supplied from both sides

clopidogrel. One day later on April 18, the DSA examination under general anesthesia showed that the thrombus in the proximal M1 segment had resolved, leaving behind a plaque with vessel wall irregularity but without significant stenosis (Fig. 1b). Endovascular treatment appeared not necessary. Only 3 days later on April 21, still under continued medication with 100 mg ASA and 75 mg clopidogrel daily, the proximal M1 segment was again narrow (Fig. 1c). We therefore decided to treat this lesion. The patient and her parents were informed about the diagnosis, the potential risks of the spontaneous course, and the treatment options, including the off-label use of a coronary balloon and an aneurysm stent—and agreed upon. Under general anesthesia the distal segment of the left internal carotid artery (ICA) and the proximal M1 segment were dilated with a Ryujin Plus OTW balloon (Terumo; 2 mm/20 mm, 8 atm). A 4.5/14-mm Enterprise stent (Codman) was deployed thereafter. The distal ICA and the proximal M1 vessel lumen were sufficiently dilated with a hemodynamically insignificant residual stenosis and a segmental narrowing of the left proximal A1 segment (Fig. 1d).

The patient continued the medication with ASA and clopidogrel and remained neurologically asymptomatic thereafter. Subsequent DSA examinations showed in-stent stenoses due to intimal hyperplasia, which were treated with conventional balloon dilatation as follows:

1. first follow-up July 7, 2008, retreatment July 23, 2008: Ryujin 2/20 mm, 10 atm, ~ 2.12 mm (Fig. 2a and 2b);
2. second follow-up September 3, 2008, retreatment September 12, 2008: Ryujin 2 mm/20 mm, 10 atm, ~ 2.12 mm (Fig. 2c and 2d);
3. third follow-up December 2, 2008, retreatment December 8, 2008: Ryujin 2.5 mm/10 mm, 8 atm, ~ 2.58 mm (Fig. 2e and 2f).

Since angiographic follow-up on January 21, 2009, again showed a significant ISR (Fig. 3a), angioplasty with a DEB was proposed to the patient. All possible options, including further observation under increased medical antiaggregation, angioplasty with a conventional balloon, deployment of a BMS or DES and temporal extra- to intracranial bypass surgery, were discussed with the patient and her family, including the related chances and risks and with explicit information about the off-label use aspects of some of these concepts. The patient finally opted for the retreatment with a DEB, which was carried out on January 26, 2009. Under general anesthesia, a 0.014″ wire (X-celerator14, ev3) was inserted into the arteria gyri angularis of the left MCA with smooth passage of the ISR in the proximal M1 segment. Predilatation (Ryujin Plus 1.5 mm/20 mm, 10 atm ~ 1.61 mm) was followed by angioplasty using the paclitaxel-eluting SeQuent Please balloon (B. Braun, Berlin, Germany;

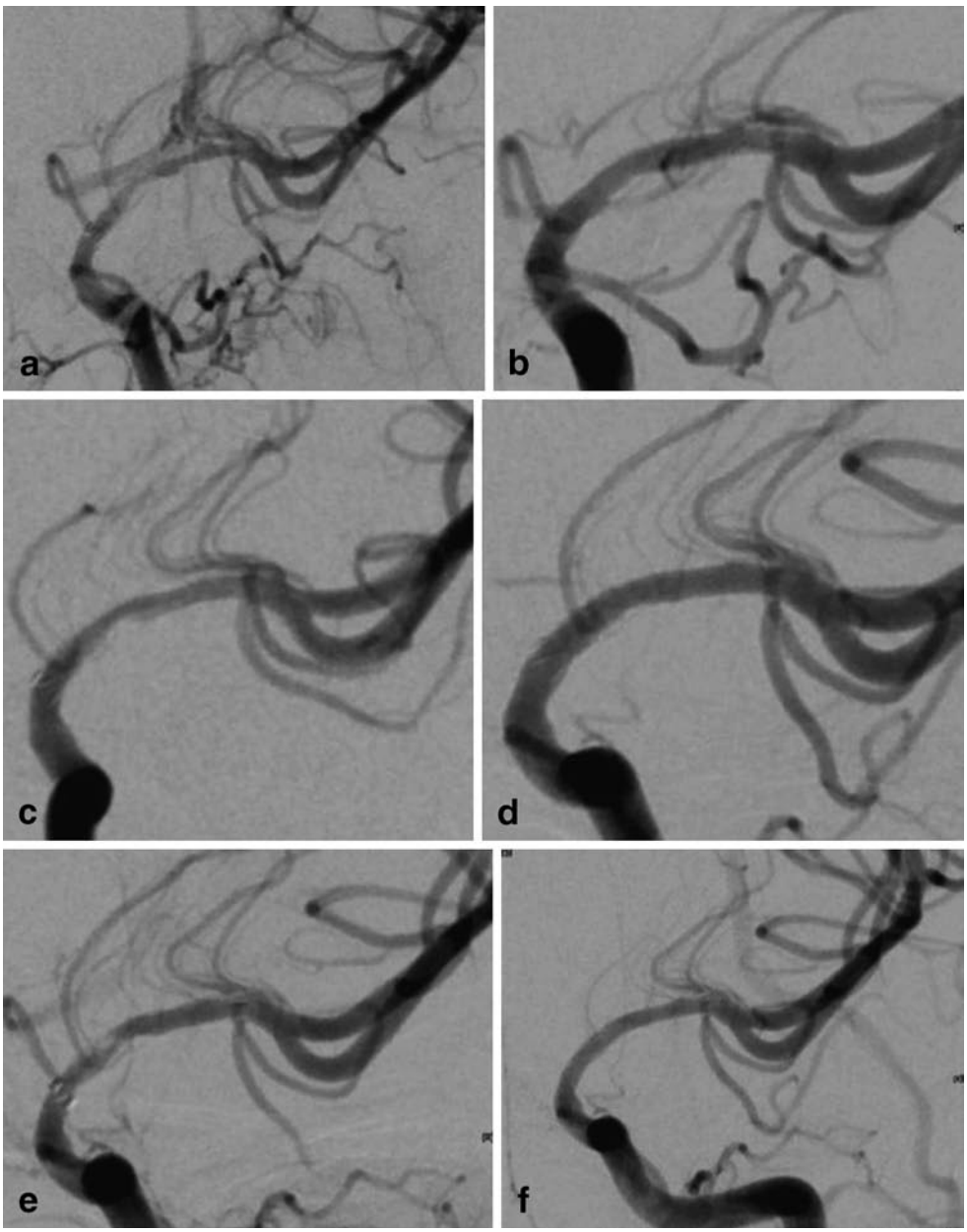

Fig. 2 Angiographic follow-up and three conventional retreatments. The three follow-up examinations were carried out 77 days (**a**), 135 days (**c**), and 225 days (**e**) after the initial treatment. Each of the three conventional balloon angioplasties was successful without any relevant residual stenoses (**b**, **d**, **f**). Only 44 days after the third conventional balloon angioplasty, the next ISR was found. In the meantime, the left proximal A1 segment was occluded without clinical sequels

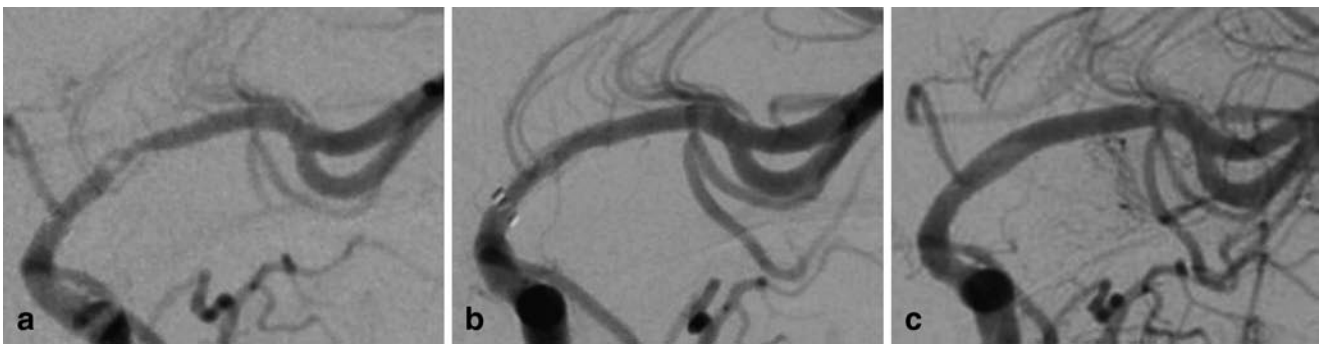

Fig. 3 ISR of the left distal ICA and proximal MCA 275 days after initial stent PTA (Enterprise) and three conventional retreatments (**a**). The ISR was treated by gentle DEB angioplasty (**b**). Further angiographic follow-up 273 days after DEB treatment showed a widely patent and smooth vessel lumen (**c**)

2 mm/20 mm, 10 atm ~ 2.13 mm, 60 s inflation time). DSA after DEB angioplasty showed a minimal residual stenosis (Fig. 3b). MRI after this treatment did not show new lesions. Four angiographic follow-up examinations, the last carried out on October 26, 2009, 273 days after the DEB procedure, confirmed persistent patency of the stent without any further intimal hyperplasia or otherwise stenosis or vessel wall abnormality. Since the initial treatment, the patient had remained free from any ischemic symptoms.

Discussion

Intracranial stent PTA can now be performed with a high level of procedural safety and efficacy [4]. The "traditional" method using balloon-expandable stents is associated with an angiographic ISR rate > 30% [2]. The combination of undersized balloon dilatation followed by the deployment of a slightly oversized self-expanding stent allows access to the target vessel even in the case of very tortuous vessel anatomy. The ISR rate, however, seems to be even higher, and these ISR are sometimes longer and tighter than the original lesion. Furthermore, the rate of another recurrence after angioplasty of an ISR is about 50% [7].

Intracranial arterial stenoses do not represent a homogeneous vessel pathology. While atherosclerosis is certainly the most frequent cause, dissection and vasculitis may well result in narrowed arteries. From a theoretical standpoint, it can be difficult if not impossible to identify the underlying pathology in a given intracranial stenosis.

Inflammation is a major factor in the pathophysiology of recurrent stenosis and intimal hyperplasia [8]. In arterial stenoses due to vasculitis, the recurrence rate after stenting is way higher than in atherosclerosis [9]. This observation is in line with the fact that stenoses of the distal ICA in young patients (sometimes without cerebrovascular risk factors and with no other atherosclerosis manifestations, insinuating vasculitis) are notorious for ISR [10].

ISR is a frequently encountered phenomenon after stent treatment of coronary atherosclerosis. For a variety of indications, a reduced ISR rate after DES deployment compared to BMS results has been shown in coronary arteries [11, 12]. Delayed acute stent thrombosis is, however, one of the issues with DES [13]. For intracranial indications, excellent follow-up results with DES have been reported [14], including the treatment of ISR after BMS deployment [15]. As a major drawback, DES are significantly less flexible than BMS, leaving many intracranial arteries just unreachable.

In 2004, Scheller et al. came up with the concept of a balloon catheter as a drug carrier [5]. On the surface of an otherwise regular balloon, the antiproliferative drug paclitaxel is fixated. Iopromide is used as an "enhancer". During balloon insertion, only minimal amounts of the drug are lost in the blood stream. The drug itself is brought in close contact with the luminal surface of the vessel intima by balloon inflation. Within 60 s of balloon inflation, about 16% of the available substance (3 μg/mm^2) are taken up by the adjacent intima. Within the smooth muscle cells, paclitaxel is a potent antiproliferative agent that inhibits cell division and migration by formation of abnormally stable microtubules [16]. This inhibition of intimal cell proliferation may last weeks and even months.

The combination of mechanical balloon dilatation and local drug application was confirmed to be very efficient for the treatment of coronary ISR [6]. Little is known if the same is true for intracranial recurrent stenoses. It may be argued that the risk of losing the paclitaxel coating of the balloon may be higher in intracranial vessels due to the tight vessel curves, which was apparently not the case in the successful treatment of the patient reported here. In the presented case, ISR could have been a self-limiting process, and the DEB was incidentally used when the power of the underlying pathology was already exhausted spontaneously. Follow-up results after redilatation of intracranial arterial stenoses have not been reported on a large-scale basis. We therefore have no comparative data available for conventional balloons. A randomized trial for the comparison of conventional balloons and DEB for the treatment of intracranial ISR would probably need a long time to get a sufficient number of cases enrolled. Paclitaxel has been shown to be effective in ISR in cardiologic patients. Their underlying disease is atherosclerosis. In the young female patient reported here, it is very likely that the etiology is not atherosclerosis, but the use of paclitaxel is still effective.

The DEB SeQuent Please is not optimized for intracranial vessels. For older patients with elongated vessels, an "over-the-wire" variant with a reduced crossing profile and a softer catheter tip would allow better access to the target lesion. Stimulated by the clinical success of the SeQuent Please, several competing products became available. They deliver antiproliferative drugs, but due to intellectual property reasons they come without or with another "enhancer" that both fixates the active substance on the balloon surface and facilitates the deposition of paclitaxel in the intimal cells.

Conclusion

Anecdotal experience shows that DEB angioplasty can be a safe and efficient treatment for intracranial ISR. Larger series and, eventually, a randomized trial have to compare conventional versus DEB dilatation. The primary use of a DEB, optimized for intracranial vessels and followed by the deployment of a self-expanding stent, might be a way to overcome the currently high rate of ISR after intracranial stenting and PTA.

Conflict of Interest Statement The authors declare that there is no actual or potential conflict of interest in relation to this article. Open Access is sponsored by B. Braun, Berlin, Germany.

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