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Early fatal hemorrhage after endovascular cerebral aneurysm treatment with a flow diverter (SILK-Stent)

Do we need to rethink our concepts?

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Abstract A 69-year-old woman presenting with short lasting recent episodes of visual impairment was treated uneventfully with a flow diverter covering the neck of a large paraophthalmic aneurysm. As angiography showed immediate flow reduction we abstained from additional coiling which was initially planned. Eleven days later CT demonstrated nearly complete thrombosis of the aneurysm. Twenty days after treatment the patient suffered a lethal subarachnoid hemorrhage after rupture of the aneurysm. All available data were reviewed and beside hemodynamic factors instability of the intra-aneurysmal thrombus is discussed as a possible cofactor leading to this disastrous event.

Keywords Cerebral aneurysm · Flow diverter · Proteolytic enzymes · SAH · Thrombus

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Introduction

Treatment of wide-necked as well as fusiform intracranial aneurysms still remains a challenge. Stent- or balloon-assisted endovascular treatment of saccular results in acceptable short-term occlusion, but the recanalization rate remains as high as 20% for small and up to 46% for large aneurysms [1–3] requiring a high number of retreatment. Even the development of coils with complex configuration or bioactive coils could not substantially solve that problem. Furthermore, filling the aneurysm sack only appears to reduce pulsatile trauma but it endures the mass effect. In the early phase after treatment induced thrombosis may, similar to coiling, lead to transient increased mass effect due to reactive perifocal changes and edema, but in the sequel the thrombus will shrink. Hemodynamic factors are thought to be implicated in the progression and rupture of intracranial aneurysms [4, 5]. The treatment of giant intracranial aneurysms ideally incorporates complete occlusion while preserving the parent artery.

Therefore the idea is obvious not to fill the excavation outside of the vessel but to reconstruct the vessel wall [6].

Stent-supported endovascular treatment with devices containing broad gaps between their struts was the first step in this direction. Investigations about redirection of flow by stents induced the development of a tighter mesh. Animal experiments could demonstrate a substantial flow reduction due to stent placement [7, 8]. Recently treatment results with Pipeline flow diverter (ev3 Company) [9, 10] and Silk flow diverter (Balt Company) have been published. There is growing experience regarding the hemodynamic interaction of this new generation of flow diverting stents.

The tight mesh of these new flow diverters raised fears that perforating vessels could be occluded when covered by the stent. Recent reports showed this fear to be unwarranted.

Different techniques have been described, such as stent deployment alone as well as stent assisted coiling of residual aneurysms. Currently, publications in journals and scientific presentations have raised high expectations for the treatment of complex saccular as well as fusiform aneurysms with flow diverters.

Case report

We present the case of a 69-year-old woman with a broad-based, paraophthalmic internal carotid aneurysm incidentally found on CT. On conventional angiography a strong cranially directed inflow could be visualized (Fig. 1). Three-dimensional-rotational angiography revealed irregularities of this saccular aneurysm which measured 15.8 mm×18.2 mm. Additional cerebral aneurysms where excluded. Due to lack of sufficient intracranial anastomoses carotid occlusion was not an option. After having been informed about the respective risks of surgical and endovascular treatment options, taking into account the age of the patient and the risks of watchful waiting, the patient consented to endovascular treatment. However, during the period of discussing treatment options and planning definitive treatment the patient developed symptoms with two short episodes of visual impairment related to the side of the aneurysm. These symptoms were interpreted as the first effects of optic nerve compression by the aneurysm.

Treatment with a flow diverter (Silk flow diverter, Balt Company) appeared to be the best option, given the progressive optic nerve impairment due to the aneurysm mass and the unfavorable flow conditions with direct flow of the main stream of the internal carotid artery into the aneurysm sack. A flow diverter with only loosely packed coils would enable a reduction of hemodynamic stress to the wall of the aneurysm and, at the same time, allow volume reduction of the aneurysm sack, as described by Fiorella et al. [10]

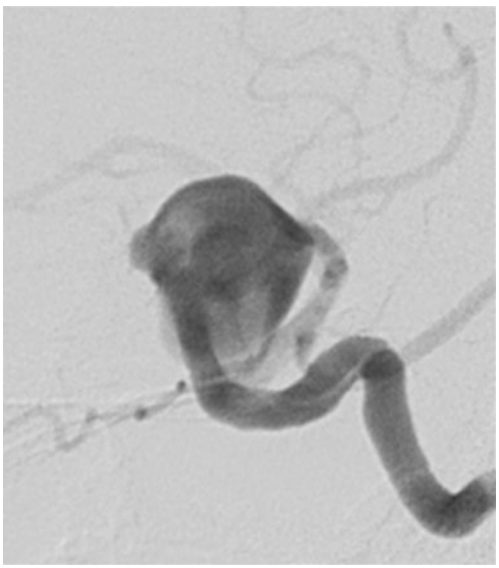

Fig. 1 Strong arterial inflow into the large paraophthalmic slightly irregular formed aneurysm

After loading with acetylsalicylacid (ASA, 100 mg daily) and clopidogrel (75 mg daily) for 5 days, flow diverter-deployment was uneventful. A coaxial system of an Arrow sheath (Arrow 7F, 80 cm) and a guiding catheter (Envoy MPD 70 cm, Cordis company) supported by a Vitek catheter (VTK 5F, 125 cm, Cordis Company) and a stiff hydrophilic guidewire (Terumo company) during passage into the common carotid artery was used to ensure a stable access to the deployment site. A microcatheter (Vasco 21, Balt Company) was placed distally to the aneurysm and flow diverter was inserted and released according to the recommendations of the company. The flow diverter (SILK 4.0×30 mm) extended from the infraophthalmic segment of the siphon up to the C1-Segment below the bifurcation into anterior and middle cerebral artery. The anterior choriod artery and the posterior communicating artery were bridged by the stent. A jailed microcatheter was removed after contrast injection under fluoroscopy showing stabile positioning of the flow diverter with somewhat decelerated contrast clearance from the aneurysm. Thirty minutes after stent deployment flow in the aneurysm was considerably reduced so that different layers of contrasted and non-contrasted blood stagnated within the aneurysm (Fig. 2).

The patient was still without symptoms after treatment. Three days later she again complained about visual impairment. The aneurysm was isodense on CT now indicating lack of thrombosis within the aneurysm. CTA showed patency of the internal carotid artery and a completely contrasted aneurysm sack (Fig. 3). Corticosteroids where given for 3 days and the symptoms disappeared.

Due to jodine in the contrast medium the patient developed mild hyperthyroidism. Preexistent instable hypertension was effectively treated pharmacologically. Five days after endovascular treatment the patient was discharged to be closely monitored and to allow more time for spontaneous delayed thrombosis of the aneurysm.

Eleven days after treatment the patient again complained of headaches. A CT-scan now demonstrated nearly the complete aneurysm to be hyper dense, indicating thrombosis within the aneurysm. There was only a small residual hypodense area at the neck of the aneurysm (Fig. 4). The density of the thrombus was notably high (66 HE). Treatment with ASA (100 mg daily) and clopidogrel (75 mg daily) was continued. Due to the fact that progressive thrombosis of the aneurysmal sac can cause headache no indication for further diagnostics (CTA, DSA) was seen.

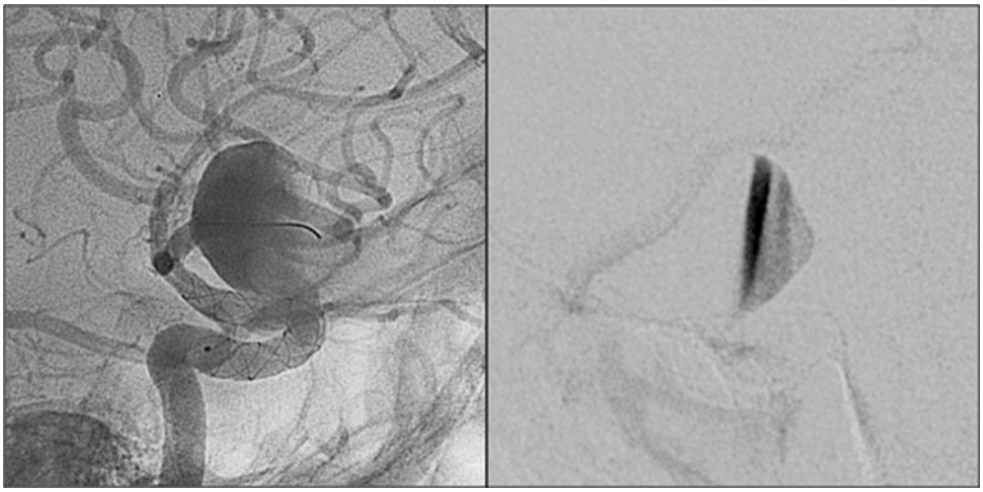

Fig. 2 Angiographic result after stent deployment (*left*) and 30 min later (*right*) showing persistent layers of contrasted and non-contrasted blood even in the late venous phase of the angiographic series as indicator of flow stagnation

Within the following days the headaches disappeared and the patient felt well without restriction of any kind. Twenty days after endovascular treatment she became comatose. CT now demonstrated extensive subarachnoid hemorrhage extending onionskin layers around the aneurysm with perifocal edema indicating a stepwise development of the disastrous outcome (Fig. 5). Within the aneurysm the isodense area was increased compared to the preceding CT. Angiography demonstrated circulation arrest in the internal carotid artery due to intracranial pressure. So source of the bleeding could not be demonstrated. Clinically the signs of brain death were observed. Blood samples of the day of rupture as well as 1 week before did not show any abnormality especially that there were no hints for infection.

Unfortunately, we could not achieve autopsy.

Discussion

The fatal outcome experienced in our patient raises questions over the concepts concerning the effects of flow diverters. These concepts and how they pertained to our patient are as follows:

1. It is assumed that a flow diverter changes blood flow and reduces aneurysm wall stress. Changed flow conditions may propagate thrombus formation. In our patient immediately after deployment of the flow diverter stagnation of blood flow was observed angiographically.
2. Flow stagnation is expected to result in aneurysm occlusion by thrombosis within the aneurysm, as also demonstrated in our patient by non-contrast CT (Fig. 4). The density of the clot was 70 (±4) HE. This density strongly indicates a high concentration of hemoglobin as an indicator for a red or statis thrombus [11]. Red thrombi are the result of stagnation of blood

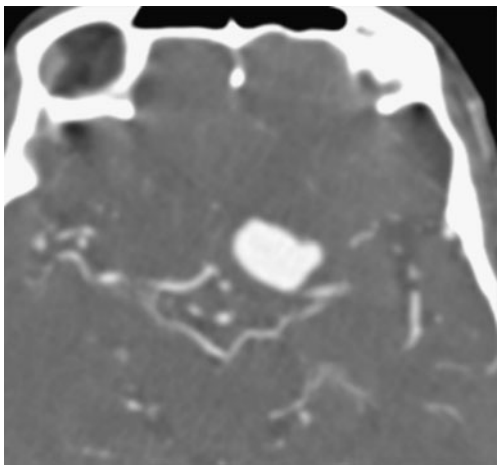

Fig. 3 CTA at day 3 showed complete perfusion of the aneurysm

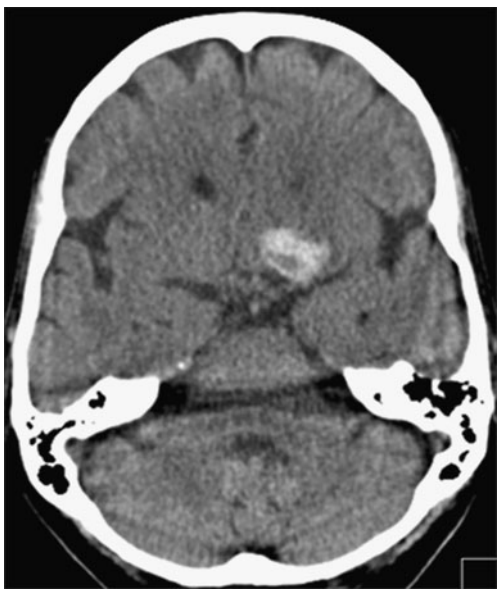

Fig. 4 Non-contrast CT at day 11 after treatment showed nearly complete thrombosis of the aneurysm. No perifocal edema could be visualized. Density measurement of the thrombus revealed a mean density of 70 (±4) HE within the thrombosed part of the aneurysm. Hypodense area adjacent to the vessel

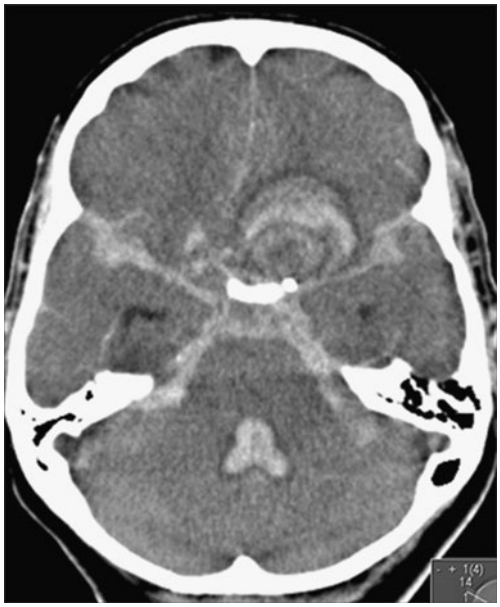

Fig. 5 CT on day20 after treatment showed extensive SAH and perianeurysmatic hematoma with slight perifocal edema. The aneurysm itself can be depicted. Within the aneurysm the isodense—non-thrombosed—area is larger than 9 days before

flow resulting in a clot containing all elements of normal blood. Red thrombi contain more enmeshed erythrocytes among sparse fibrin strands compared to precipitation or white thrombi. White thrombi tend to have gross and microscopic lamination (lines of Zahn) produced by pale layers of platelets and fibrin alternating with darker red cell-rich layers.

3. Thrombosis is expected to be followed by thrombus organization and fibrosis, which is mediated by invading inflammatory cells and fibrocytes. This process normally begins 48 h after thrombus formation.

Obviously, organization of the thrombus did not occur in our patient, resulting in a fatal outcome 20 days after implantation of the flow diverter. Rather, the growing hypodense area within the aneurysm shows replacement of hyperdense thrombotic material. Whether this replacement is a consequence of recurrent inflow with compression or displacement of thrombus or it is thrombolysis may not be differentiated. But both options have to be discussed. In addition, perifocal edema exceeding the extent we would have expected for acute aneurysm rupture may indicate subacute development of wall instability which preceded the fatal rupture. Aneurysm rupture per se was difficult to explain by hemodynamic stress only since angiographically there was no or extremely reduced flow within the aneurysm (Fig. 2). CT did not give any hint for a change of the position or the configuration of the flow diverter. Changed configuration of the flow diverter after rupture has to be related to the elevation of intracranial pressure.

We hypothesize that reduced resistance of the aneurysm wall—perhaps not alone but as a cofactor together with residual flow—might serve to explain the rupture of the aneurysm after implantation of the flow diverter, possibly due to the biochemical characteristics of the resolving thrombus.

In this context it is known that red thrombi are more lysable than white thrombi [12–15]. Due to the leucocytes contained within the red thrombus [16, 17] the activity of lytic enzymes such as elastase is higher in red compared to white thrombi. Bendszus et al. [18] published a similar case of a fatal recurrent subarachnoid hemorrhage after complete endovascular aneurysm occlusion. Histologically, the authors state, no "signs of tissue response as thrombus organization…, or fibrin formation" were found. This finding was argued to be in contrast to the normal course after endovascular treatment of aneurysms with coils where fibrin and macrophages within the aneurysm are found. It was hypothesized that lack of formation of an organized thrombus was the reason for rerupture. This may occur in certain cases based on a reduced biological answer to the coils and consequently bioactive coils were propagated.

In our case CT indicated a non-organized red thrombus. We do not know about the biological reactivity in our particular patient and perhaps factors related to reduced biological reactivity in our patient played an additional role. However, immediate flow stagnation alone could be a reasonable explanation for the development of a non-organized red thrombus. The red thrombus is physiologically instable and has a high content of proteolytic enzymes which in turn weaken the wall of the aneurysm.

Another factor possibly contributing to rupture may have been the individual anatomy in our patient with a very sharp turn of the internal carotid artery at the base of the aneurysm. The physiologic high flow in the internal carotid artery in combination with a fenestrated stent which was permeable for blood may not have reduced the flow at the neck of the aneurysm completely, resulting in residual hemodynamic forces in the occipital aspect of the aneurysm neck. Here we stipulate the rupture to have occurred anatomically.

Anti-aggregation therapy can be assumed to have played an additional role just before rupture, preventing platelet aggregation before and during extravasation of blood from the ruptured aneurysm. Antiplatelet therapy is without any doubt necessary to prevent thromboembolism, our own experience being in accordance with the widely accepted conviction which prohibits a reduction of antiplatelet therapy in this early stage after stent implantation. Therefore, antiplatelet therapy raises a dilemma when the aneurysm is not excluded completely after stents or flow diverters are placed because these regimens may increase the risk of disastrous hemorrhage.

In summary rupture cannot be explained conclusively only by one factor. We hypothesize multiple factors working synergistically to have resulted in the disastrous outcome witnessed in our patient. Formation of an instable red thrombus after abrupt blood stagnation in the aneurysm and high concentration of lytic enzymes generated by captured leucocytes together with the well-known inflammatory perianeurysmal changes may have destabilized the aneurysm wall. Partial thrombolysis and weakening of the aneurysm wall opened a route between thrombus and wall of the aneurysm for residual flow due to the sharp curve of the vessel at the neck of the aneurysm. Edema around the aneurysm indicated that this process occurred over a number of days. We are convinced that interruption of this chain of disaster at any point could have prevented early rupture

Nevertheless, we are positive about the idea of wall reconstruction by flow diverting devices which should be developed further. For the present, however, the available technique in particular cases results in up to so far inexplicable failures. Fatal results are an obligation to check all aspects of a therapeutic device. Indication, technical aspects (i.e., additional coiling, telescope technique), anti-aggregation, etc. have to be put into question and critically analyzed. Perhaps there will be found indications, which are not suitable for that treatment and others which will be treated more successfully with flow diverters than with any other means.

Perhaps achieving a more fibrin-containing thrombus may reduce probability of such events. We are thinking about additional coiling, but we know that there already have been reported similar events even despite additional coiling. Our hope would be to produce an organized white thrombus with accumulated fibrin which may prevent immediate contact of lytic enzymes with the wall of the aneurysm in this early phase after treatment. In fusiform aneurysms, on the other hand, additional coils may not be an option due to the risk of occluding perforators (i.e., in the basilar artery).

Conflict of interest statement We declare that we have no conflict of interest.

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