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Ruptured Fisher grade 3 blister aneurysms have a higher incidence of delayed cerebral ischemia than ruptured Fisher grade 3 saccular aneurysms

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Abstract:

BACKGROUND: Blister aneurysms are a rare subclass of aneurysms, which remain challenging to treat both with open cerebrovascular and endovascular techniques, and clinicians continue to see poor outcomes in some cases despite improvements in technology. Based on our clinical observations, we hypothesized that patients with a Fisher grade 3 subarachnoid hemorrhage (SAH) from a ruptured anterior circulation blister aneurysm are significantly more likely to develop poor outcome due to delayed cerebral ischemia than patients with a Fisher grade 3 SAH from a ruptured anterior circulation saccular aneurysm.

METHODS: In this consecutive case series, we reviewed management, outcomes, and rates of delayed cerebral ischemia for all ruptured anterior circulation blister aneurysms from 2012 to 2018 at our institution and compared them to a concurrent cohort of ruptured saccular anterior circulation aneurysms. A blister aneurysm was defined as an aneurysm that arises from a nonbranching point and demonstrates hemispherical anatomy on diagnostic angiography.

RESULTS: We identified 14 consecutive ruptured anterior circulation blister aneurysms. Thirteen aneurysms were treated operatively– 5 with clip remodeling and 8 with flow diversion embolization. While clip remodeling had a high intraoperative rupture rate (80%), there was only one (12.5%) intraoperative rupture with flow diversion embolization. Outcomes were worsened by delayed cerebral ischemia from vasospasm in patients with Fisher 3 hemorrhages from blister aneurysms (86%). The rate of delayed cerebral ischemia from vasospasm was significantly higher for ruptured blister aneurysms than for a concurrent cohort of ruptured saccular aneurysms (8.6%, $P = 0.0001$).

CONCLUSION: Ruptured Fisher grade 3 anterior circulation blister aneurysms have a significantly higher incidence of delayed cerebral ischemia from vasospasm compared to saccular aneurysms, regardless of the treatment modality.

Keywords:

Blister aneurysm, clipping, delayed cerebral ischemia, flow diversion embolization, saccular aneurysm, stroke, vasospasm

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Introduction

Most intracranial aneurysms are saccular aneurysms, which arise from arterial branching points. A saccular aneurysm consists of all layers of the vascular wall, which may be further strengthened by collagenization.[1] The wall thickness of a saccular aneurysm is inversely proportional to its size, according to Laplace's law. In contrast, a blister aneurysm is a defect at a nonbranching point in the arterial wall

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covered by a thin layer of the fibrous clot, which has little strength.[2]

The incidence of blister aneurysms is low and has been reported between 2.1% and 7.3% of all treated aneurysms.[3,4] Ruptured anterior circulation blister aneurysms were conventionally treated with open cerebrovascular techniques either by covering the arterial wall defect with an encircling clip, wrapping, approximating the normal edges of the defect with direct clipping (clip remodeling) or by trapping and bypass.[5,6] In recent years, these aneurysms have been increasingly treated with flow diversion embolization.[7]

Significant intraoperative complication rates and a high percentage of poor outcomes have been reported in several studies for the treatment of blister aneurysms with open cerebrovascular techniques.[8-10] Similarly, poor outcomes can also be seen in ruptured blister aneurysms that are treated with endovascular techniques such as flow diversion.[11] Based on our clinical observations, we hypothesized that one of the drivers of poor outcomes in ruptured blister aneurysms is delayed cerebral ischemia and that a patient with Fisher grade 3 subarachnoid hemorrhage (SAH) from a ruptured anterior circulation blister aneurysm has significantly higher odds of developing symptomatic delayed cerebral ischemia than a patient with a ruptured saccular aneurysm in the same category.

Methods

The study was approved by the institutional review board (IRB) of our institution (IRB #953464-1). The IRB did not require patient consent for this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

A blister aneurysm was defined as an aneurysm that arises from a nonbranching point and has a hemispherical shape on diagnostic angiography (neck size > dome size). Clip remodeling was defined as a direct approximation of the edges of the blister aneurysm wall defect with a Sugita clip (Mizuho, Union City, California) or the treatment of the wall defect with an encircling Sundt clip (Mizuho, Union City, California). Muslin (D and H Wholesale Medical Inc., Ruston, Louisiana) wrapping was initially performed in one patient by buttressing a ball of Muslin gauze between the pia of the optic tract and the blister aneurysm. A cotton-clipping technique was employed in one patient by placing a cottonoid patty without a string over the hole in the artery and securing it with a clip. Stenting was performed with the Pipeline® Embolization Device (Medtronic, Minneapolis, Minnesota), an Enterprise® stent (Codman Neuro, Fremont, California), or an LVIS Jr., stent (Microvention, Aliso Viejo, California). For flow diversion embolization, patients were loaded with 300 mg clopidogrel and 325 mg aspirin and maintained on 75 mg clopidogrel and 325 mg aspirin daily.

We performed a retrospective review of all ruptured anterior circulation blister aneurysms treated between 2012 and 2018 and recorded patient age, gender, Hunt and Hess grade, Fisher grade, blister aneurysm location, treatment modality, incidence of delayed cerebral ischemia from vasospasm, modified Rankin score, and length of follow-up. In the same period, we also recorded the Fisher grade and incidence of delayed cerebral ischemia in patients with ruptured saccular anterior circulation aneurysms. At our institution, all aneurysmal SAH patients are monitored in the Neurological Intensive Care Unit; nursing and medical staff adhere to a strict set of protocols for identifying delayed cerebral ischemia: focal (hemiparesis, aphasia, hemianopia, or neglect) or global neurological impairment (≥2 points of decline in Glasgow Coma Scale) lasting for at least 1 h and/or cerebral infarction which is not immediately apparent after aneurysm occlusion, attributable to ischemia and is not attributed to other causes (surgical complication, metabolic derangements) after appropriate clinical, imaging, and laboratory evaluation.[12] Patients who died or were transferred to another facility within 14 days of presentation were excluded from the vasospasm analysis, except if the patient already presented with delayed cerebral ischemia due to vasospasm on admission. The incidence of delayed cerebral ischemia was compared between patients with ruptured anterior circulation blister and saccular aneurysms in patients who survived >14 days after admission or presented with delayed cerebral ischemia due to vasospasm on admission using Fisher's exact test. A P value of <0.05 was considered statistically significant.

Results

In the analysis of clinically significant vasospasm rates in our saccular and blister aneurysm cohorts, we identified 65 patients with Fisher grade 3 hemorrhages, of which 58 were saccular aneurysms and 7 were blister aneurysms. The delayed cerebral ischemia rate in the blister cohort was 86% (6 of 7 patients) and 8.6% in the saccular cohort [5 out of 58 patients; Figure 1]. We used Fisher's exact test to show that patients with Fisher grade 3 hemorrhages from ruptured anterior circulation blister aneurysms were significantly more likely to develop delayed neurological deficits from vasospasm than patients with Fisher grade 3 hemorrhages from ruptured anterior circulation saccular aneurysms [P = 0.0001; Table 1].

Of the 14 patients with ruptured anterior circulation blister aneurysms, no treatment was offered to one patient due to Hunt and Hess grade 5 presentation and multiple comorbidities. For the remaining 13 patients, five patients underwent clip remodeling and eight patients underwent flow diversion embolization or stenting [Table 2]. One patient initially underwent Muslin wrapping but was re-operated after 20 days due to aneurysmal growth on subsequent imaging. With clip remodeling, four of five operations were complicated by the intraoperative rupture of the blister aneurysm. The intraoperative rupture was successfully treated in one patient with a Sundt clip. In contrast, two patients progressed to brain swelling due to hemispheric stroke, and clip remodeling of the aneurysm had to be aborted. The fourth patient underwent clip remodeling without intraoperative rupture [Figure 2], while the fifth patient underwent a cotton-clipping technique after intraoperative rupture for an M2 bifurcation blister aneurysm but rebled on the postoperative day 1.

Table 1: Fisher's exact test of clinically significant vasospasm rates between ruptured Fisher grade 3 blister aneurysms and ruptured Fisher grade 3 saccular aneurysmsa

	Fisher's exact test	
	# Saccular aneurysms	# Blister aneurysms
Vasospasm	5	6
No vasospasm	53	1
Fisher's test statistic	Value = 0.0001, significant at $P < 0.05$	

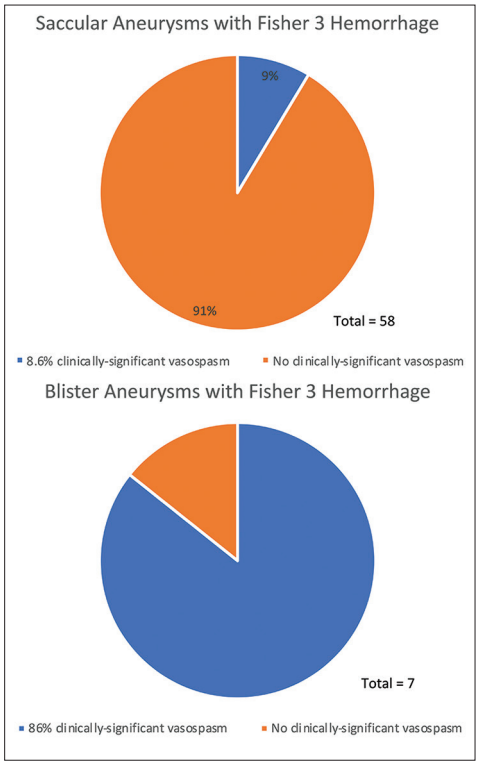

Figure 1: Difference in delayed cerebral ischemia between ruptured Fisher grade 3 blister and saccular aneurysms. Comparison of the incidence of delayed neurological deficits from vasospasm in Fisher grade 3 ruptured saccular aneurysms (upper panel) and Fisher grade 3 ruptured blister aneurysms (lower panel). Fisher's exact test showed that patients with Fisher grade 3 ruptured blister aneurysms were significantly more likely to develop delayed neurological deficits from vasospasm than patients with Fisher grade 3 ruptured saccular aneurysms ($P = 0.0001$)

Eight patients were treated with endovascular techniques in the blister aneurysm cohort. Six patients underwent placement of a Pipeline® flow diversion device [Figures 3 and 4], one patient underwent placement of an Enterprise® stent, and another patient underwent placement of an LVIS Jr., stent. There was one intraoperative complication in a patient who was admitted with severe right middle cerebral artery (MCA) vasospasm and a right supraclinoid blister aneurysm. An LVIS Jr., stent placement across the blister aneurysm led to occlusion of the right MCA, which was followed by an intraoperative aneurysmal rupture after Integrilin and tPA administration requiring carotid artery

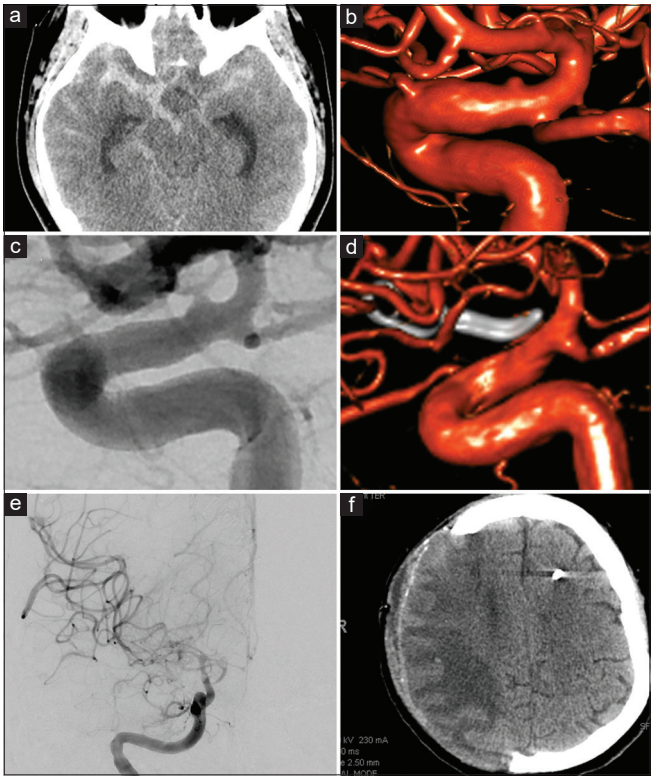

Figure 2: Clip remodeling of a ruptured Fisher grade 3 blister aneurysm followed by severe vasospasm and delayed cerebral ischemia. The patient is a 43-year-old woman who complained of a severe headache since the prior day and presented with a Hunt and Hess 2, Fisher 3 subarachnoid hemorrhage (a) from a ruptured right internal carotid artery trunk blister aneurysm (b and c). Patient underwent a right frontotemporal craniotomy and clip approximation of the normal edges of the defect (d). On hospital day 6, she developed severe right-sided vasospasm (e), was placed on induced hypertension therapy and underwent daily intra-arterial verapamil injections. Despite therapy, she progressed to a large right-sided stroke with midline shift and underwent a right hemicraniectomy on hospital day 8 (f). A right cranioplasty was performed 8 months later, and she recovered to modified Rankin scale 4

Table 2: Incidence of delayed cerebral ischemia and outcomes in patients who presented with ruptured blister aneurysms at our institution

n	Sex	Age	Hunt and Hess	Fisher	Aneurysm location	Treatment modality	Procedural complication	DCI	mRS	F/u (months)
1	Male	38	2	2	ICA trunk	Sundt clip	Rupture	No	1	12
2	Female	56	3	3	ICA trunk	Attempted clipping	Rupture, stroke	N/A	6	N/A
3	Female	43	2	3	ICA trunk	Clipping	None	Yes	4	9
4	Male	37	2	2	ICA trunk	Enterprise stent	None	No	1	6
5	Male	54	3	3	ICA trunk	Muslin wrapping Attempted clipping	Rupture, stroke	Yes	6	N/A
6	Male	62	2	3	ICA trunk	Flow diversion with pipeline	None	No	0	7
7	Male	43	2	3	M1 segment	Flow diversion with pipeline	None	Yes	6	N/A
8	Male	47	3	3	ICA trunk	Flow diversion with pipeline	None	Yes	6	N/A
9	Male	54	5	3	ICA trunk	None	N/A	N/A	6	N/A
10	Female	42	1	2	ICA trunk	Flow diversion with pipeline	None	No	0	6
11	Female	32	3	2	ICA trunk	Flow diversion with pipeline	None	No	0	6
12	Female	49	3	3	ICA trunk	Attempted clipping Flow diversion embolization with Pipeline	Rupture	Yes	0	6
13	Female	73	2	3	ICA trunk	Attempted flow diversion with LVIS Jr. stent Carotid artery deconstruction with coiling	Stent occlusion, intraoperative aneurysmal rupture after Integrilin and tPA, anterior choroidal artery stroke	Yes	6	N/A
14	Male	63	1	3	M2 bifurcation	Cotton-clipping technique	Rebleed on POD#1	N/A	6	N/A

ICA: Internal carotid artery, N/A: Not available, POD: Postoperative day, DCI: Delayed cerebral ischemia

deconstruction with coil embolization. Several days later, the patient progressed to diffuse cerebral vasospasm and stroke, and care was withdrawn. Follow-up diagnostic angiography showed complete occlusion of the aneurysm in 5 out of 6 patients treated with the Pipeline® Embolization Device, while the patient treated with an Enterprise® stent continued to show filling of the aneurysm after 6 months. No patient experienced a delayed re-rupture of the blister aneurysm until the last follow-up. No clinically significant hemorrhages around external ventricular drain tracts were observed in the setting of dual anti-platelet therapy.

For analysis of the incidence of delayed cerebral ischemia in ruptured anterior circulation blister aneurysms, three out of the fourteen aneurysms needed to be excluded due to withdrawal of care within 14 days of admission. None of these three patients developed delayed cerebral ischemia from vasospasm before the withdrawal of care. Among the ruptured anterior circulation blister aneurysms which qualified for the study, there were four Fisher grade 2 hemorrhages and seven Fisher grade 3 hemorrhages. Six of the seven patients with Fisher grade 3 hemorrhages developed or presented with clinically significant vasospasm [86%; Figure 4].

Between July 2012 and September 2017, 88 patients presented at our institution with ruptured anterior circulation saccular aneurysms. Four patients needed to be excluded due to withdrawal of care or transfer to another facility within 14 days. None of the excluded aneurysms developed vasospasm at our institution. Among the ruptured anterior circulation saccular aneurysms that qualified for the study, there were 18 Fisher grade 2 hemorrhages, 58 Fisher grade 3 hemorrhages, and 8 Fisher grade 4 hemorrhages. None of the patients in the Fisher grade 2 and 4 cohorts developed clinically significant vasospasm, whereas 5 of the 58 patients in the Fisher grade 3 cohort developed clinically significant vasospasm [8.6%; Table 3].

Discussion

In our analysis of both cohorts of ruptured anterior circulation Fisher grade 3 blister aneurysms and saccular aneurysms, we found that ruptured anterior circulation Fisher grade 3 blister aneurysms had a significantly higher risk of delayed cerebral ischemia than saccular aneurysms. It is unclear why blister aneurysms with Fisher grade 3 SAH in our series were associated with such a high rate of delayed cerebral ischemia. Blister aneurysms have been associated with a wide variety of etiologies such as hypertension, dissection, and atherosclerosis. There are reports that an infection can increase the likelihood of delayed cerebral ischemia after SAH.[13,14] Ogawa *et al*. reported on the proliferation of *Aspergillus* hyphae in the wall of a blister aneurysm.[15] However, Ishikawa *et al*. noticed no infiltration of inflammatory cells near the defect in one patient with a blister aneurysm, but only degeneration of the internal elastic lamina.[16] Some fungi have been shown to have elastolytic activity.[17] Patient no. 9 in our

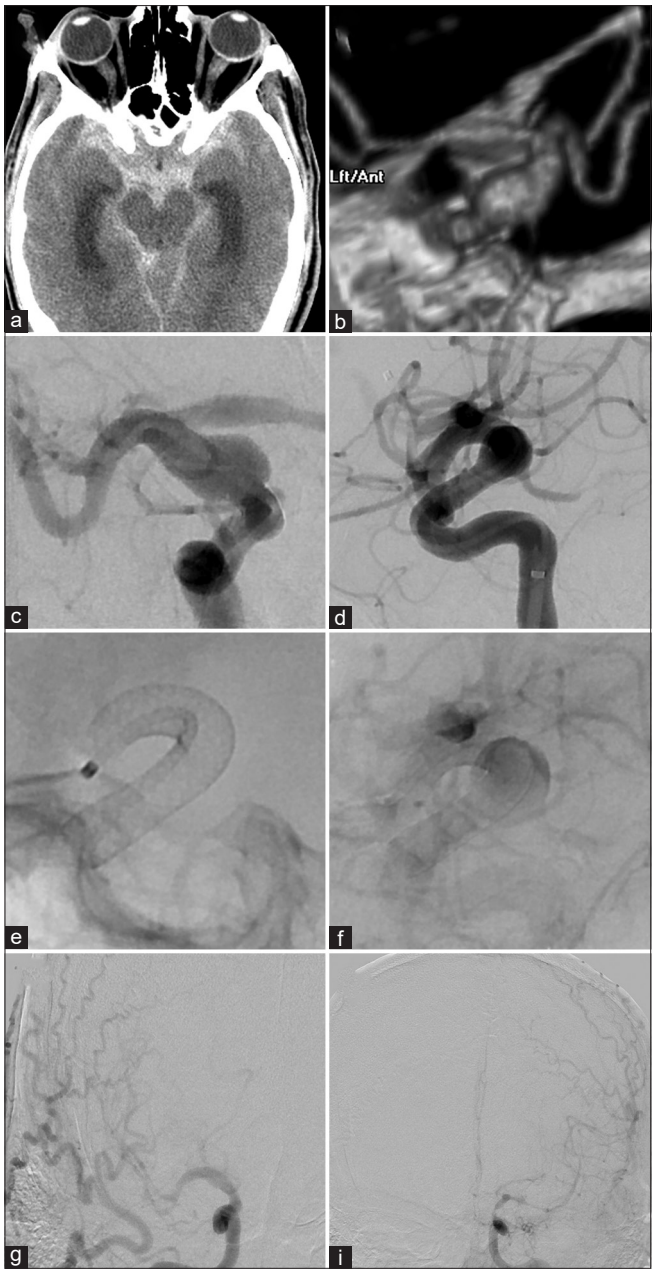

Figure 3: Flow diversion embolization of a ruptured Fisher grade 3 blister aneurysm followed by severe vasospasm and delayed cerebral ischemia. A 47-year-old male with HIV, substance abuse, hypertension and asthma became unconscious and later had a seizure. He was intubated in the field. He presented as a Hunt and Hess 4, Fisher 3 subarachnoid hemorrhage (a). CT angiography of the brain showed a right internal carotid artery trunk blister aneurysm (b). He underwent placement of a lumbar drain for hydrocephalus and was loaded with aspirin and clopidogrel in preparation for flow diversion embolization. Intraoperative AP (c) and lateral (d) digital subtraction angiography imaging showed the presence of a dorsal wall internal carotid artery trunk blister aneurysm. The aneurysm was treated with a Pipeline® flow diversion device (lateral view; e) resulting in faint layering of contrast in the dome (eclipse sign; f). The patient followed commands on hospital day 4 and was extubated. His exam rapidly declined on hospital day 8, and he became comatose. Diagnostic cerebral angiography showed occlusion of the aneurysm (g), but bilateral severe anterior circulation vasospasm (g and i). Due to multiple strokes, the family elected to withdraw care (modified Rankin Scale 6)

series was diagnosed at autopsy with mucor hyphae and conidia at the site of his blister aneurysm formation.[18]

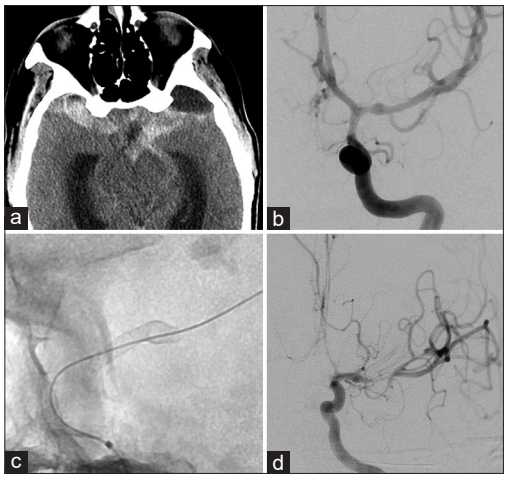

Figure 4: Flow diversion embolization of a ruptured Fisher grade 3 blister aneurysm followed by severe vasospasm and delayed cerebral ischemia. 43-year-old male with remote history of hemicraniectomy for TBI with baseline wheelchair-dependence presented as a Hunt and Hess 1, Fisher 3 subarachnoid hemorrhage (a). Diagnostic cerebral angiography revealed a fusiform blister aneurysm of the left M1 segment (b). He was loaded on aspirin and clopidogrel and underwent placement of a Pipeline® embolization device across the aneurysm from the left M1 segment to the supraclinoid internal carotid artery (c). He developed worsening hydrocephalus on postoperative day 1 and underwent uncomplicated placement of a lumbar drain. On hospital day 4, the patient developed vasospasm (d) and underwent five intra-arterial verapamil injection procedures. He progressed to develop bilateral ACA territory infarctions, and the family decided to withdraw care considering his diminished baseline functional capacity (modified Rankin Scale 6)

Although HIV-associated intracranial aneurysms have conventionally been described in children, more recent publications have also described them in adults.[19] One of the patients in our blister cohort was HIV positive, and it is possible that HIV-related vasculopathy played a role in both blister aneurysm formation and delayed ischemia in this patient [Figure 3]. HIV-related vasculopathy is increasingly recognized as a distinct entity and has been associated with fusiform or more irregular morphologies than the traditional saccular kind.[20] It is reasonable to assume that some blister aneurysms were associated with infection in this series, which increased the chance of delayed cerebral ischemia from vasospasm.

The question arises whether treatment technique has an impact on delayed cerebral ischemia rate since open cerebrovascular surgery was associated with a high intraoperative rupture risk in our series (80%), and more subarachnoid blood theoretically increases the risk of delayed cerebral ischemia even though most of the blood is aspirated immediately at the time of surgery through suction. However, aneurysm re-rupture has been independently associated with delayed cerebral ischemia.[14] Table 3 shows the incidence of vasospasm and outcomes per case with different treatment modalities in our series. Clip remodeling of ruptured anterior circulation blister aneurysms carries a high

Table 3: Incidence of clinically significant vasospasm among different fisher grades for saccular aneurysms and blister aneurysms

Ruptured anterior circulation saccular cohort			Ruptured anterior circulation blister cohort		
Fisher grade	# of patients	# of patients w/ vasospasm	Fisher grade	# of patients	# of patients w/ vasospasm
Fisher 2	18	0	Fisher 2	4	0
Fisher 3	58	5	Fisher 3	7	6
Fisher 4	8	0	Fisher 4	0	0
Total	84	5	Total	11	6

morbidity and mortality risk.[8-10] Ogawa *et al*. reported in a case series of open cerebrovascular treatment of ruptured blister-type aneurysms intra- or postoperative ruptures in 15 out of the 40 patients, and slightly <50% of patients experienced a good outcome.[10] Konczalla reported unfavorable outcome in 52% of cases treated with open cerebrovascular techniques.[21] Flow diversion embolization is increasingly performed for ruptured anterior circulation blister aneurysms with good outcomes.[7,22-25] A delayed re-rupture of a flow-diverted blister aneurysm was reported by Mazur *et al*.[26] We observed no recurrent ruptures during our follow-up period with endovascular techniques. However, we also observed a poor outcome due to delayed cerebral ischemia in two cases in patients treated with Pipeline® flow diversion embolization only, so there may be an inherent risk of blister aneurysms to cause delayed cerebral ischemia, independent of the treatment modality.

Conclusion

Blister aneurysms causing a Fisher 3 SAH have a higher incidence of delayed cerebral ischemia from vasospasm compared to saccular aneurysms, regardless of treatment modality. Further research is necessary to determine the underlying cause of the increased delayed cerebral ischemia rates with ruptured blister aneurysms.

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Conflicts of interest
There are no conflicts of interest.

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