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CASE REPORT - VASCULAR NEUROSURGERY - ARTERIOVENOUS MALFORMATION

Resection of a posterior fossa arteriovenous malformation complicated by leaked Onyx: a case report and review of literature

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Abstract

Extravasation of Onyx is a rare complication during embolization of arteriovenous malformations (AVM). We present a case of embolization that was complicated by leakage of Onyx into the cerebellum which was later encountered during surgical excision of the AVM. Our goal is to report this rare event and to outline successful treatment of this complication. The patient's records were reviewed for medical history, laboratory and radiologic workup, and outpatient clinical follow-up. A 62-year-old female presented with Hunt Hess grade 2 and modified Fisher grade 2 subarachnoid hemorrhage (SAH) secondary to ruptured left posterior inferior cerebellar artery (PICA) aneurysm associated with a superior cerebellar vermian AVM. Following endovascular intervention, the aneurysm was completely embolized; however, only 75% of the AVM could be safely obliterated. Extravasation of Onyx from the ruptured aneurysm was noted on her initial angiogram. Elective suboccipital craniectomy was subsequently planned for resection of the residual AVM where the extravasated Onyx posed an operative nuisance during resection. Post-op angiogram confirmed complete resection of the AVM, as well as the bulk of the extravasated Onyx. Patient did well post-operatively, remaining neurologically intact throughout her hospital course. Although infrequently reported in the literature, Onyx extravasation is a potential complication that neurosurgeons should be ready to face. Adherence of Onyx to surrounding parenchyma could hinder optimal surgical resection of AVM and increase complications. Therefore, careful surgical dissection should be performed with special care to delicate neurovasculature. In this case, complete resection of the AVM and Onyx mass was safely achieved.

Keywords Onyx leakage · Endovascular · Arteriovenous malformation · Complication

Background and importance

Embolization with Onyx is commonly used in the treatment of intracranial vascular lesions, both as primary treatment and as adjuvant to radiation and/or surgical resection. The liquid embolic agent Onyx (ev3 Neurovascular, Irvine, CA) is a non-adhesive, radiolucent compound consisting of an ethylene-vinyl alcohol copolymer suspended in dimethyl sulfoxide (DMSO) [2]. Once it is injected and in contact with water (i.e., plasma), Onyx precipitates and forms a cast. When combined with tantalum, it is rendered radiolucent, enabling fluoroscopic visualization. It was first developed in the 1990s and approved by the FDA for treatment of intracranial arteriovenous malformations (AVMs) [19, 21, 23], and its use has become widespread ever since.

Although Onyx has been shown to be generally safe and effective in the treatment of intracranial AVMs, technical complications including vascular dissection, stuck microcatheter, and unintended vessel embolization may occur [8, 22]. However, reports of extravasated Onyx being encountered during surgical resection of pre-operatively embolized AVMs are rare. Here, we report a case in which Onyx extravasated from a ruptured aneurysm associated with an AVM that was later visualized intraoperatively.

This article is part of the Topical Collection on *Vascular Neurosurgery – Arteriovenous malformation*

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Clinical presentation

History and examination

The patient is a 62-year-old woman who initially presented to an outside hospital complaining of severe headache, nausea, vomiting, and visual disturbances. Her past medical history included Waldenstrom macroglobulinemia, alcohol use, and anxiety. She had no family history of arteriovenous malformation or aneurysm. On CT head, the patient was found to have Hunt Hess grade 2 and modified Fisher grade 2 (HH2mF2) subarachnoid hemorrhage, with intraventricular hemorrhage (IVH) primarily in the fourth ventricle (Fig. 1). Patient was subsequently transferred to our institution for further management. Upon arrival, she continued to complain of these symptoms. On exam, she was neurologically intact with a Glasgow Coma Score (GCS) of 15. CTA showed a left posterior inferior cerebellar artery (PICA) aneurysm and a posterior cerebellar vermian AVM. The patient underwent diagnostic angiography which showed a 2.5-cm vermian AVM, as well as a ruptured 3-mm mid-left PICA aneurysm (Fig. 2). The aneurysm, which was identified as the source of hemorrhage, was supplied mainly by distal branches of the left PICA and left superior cerebellar artery, with a smaller amount of blood supply coming from distal branches of the right PICA. Venous drainage into the torcula and right transverse sinus was also noted.

Embolization procedure

After visualization of the AVM and aneurysm on angiogram, embolization was performed. Using roadmap technique, a CAT 5 guide catheter with a Scepter balloon and Synchro standard wire were guided into the left vertebral artery. The balloon and wire were then maneuvered into the midportion of the left PICA. The balloon was inflated proximally to the ruptured left PICA aneurysm. The aneurysm and distal AVM were then embolized using Onyx 18. Onyx extravasated from the ruptured left PICA aneurysm and was seen along the surface of the cerebellum and within the fourth ventricle. Complete embolization of the left PICA aneurysm and 75% embolization of the AVM were achieved (Fig. 3). After embolization, angiography demonstrated minimal residual supply to the AVM from the bilateral superior cerebellar arteries and mild residual supply from the distal right PICA. Angio-Seal closure device was deployed at the bilateral femoral artery access sites, and complete hemostasis was achieved. Patient tolerated the procedure well and was neurologically intact on exam post-procedure. Notably, although her initial CT head demonstrated minimal hydrocephalus, later on in her hospital course, she was found to have significant hydrocephalus causing altered mental status. A ventriculoperitoneal shunt was then placed which restored the patient's mental status back to baseline. At discharge, the patient's symptoms improved except for nausea which was prescribed antiemetics. On follow-up 1 month later, the patient reported normal return to daily activities but persistent nausea unresponsive to medication. To treat the residual AVM, the option of gamma knife radiosurgery versus surgical resection was discussed with the patient and she opted for surgery.

Operative course

Suboccipital craniectomy was planned for resection of the residual AVM by the senior author. During surgery, extravasated Onyx was encountered at the site of the AVM. The Onyx was very adherent to the surrounding blood vessels, making it difficult to dissect around the Onyx mass. Ultimately, gross total resection of the AVM as well as the bulk of Onyx was completed, and adequate hemostasis was achieved. Gross and histopathologic findings are shown in Figs. 4 and 5.

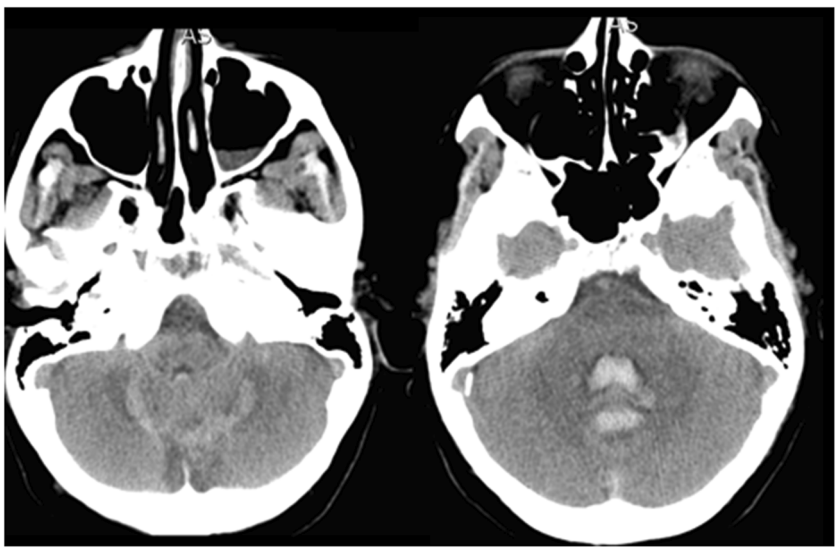

Fig. 1 Patient's initial CT head, demonstrating subarachnoid hemorrhage in the posterior fossa, with hemorrhage into the fourth ventricle

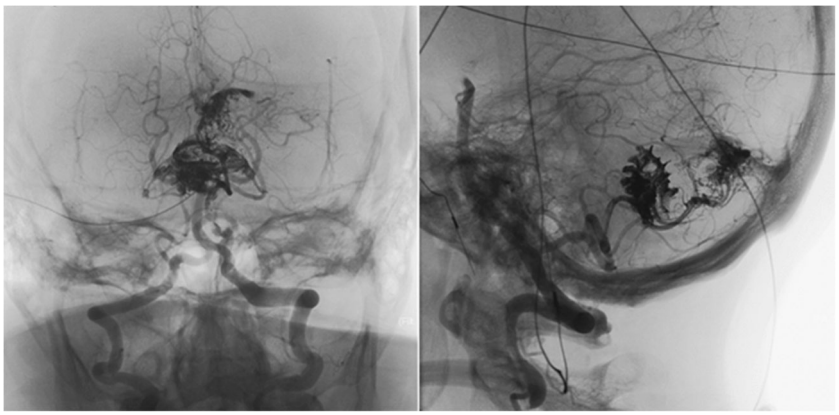

Fig. 2 Cerebral angiogram demonstrating a ruptured left PICA aneurysm and arteriovenous malformation supplied primarily by the left PICA and left superior cerebellar artery

Histologic examination showed abnormal tangles of arteries and veins without intervening capillaries characteristic of AVMs (Fig. 4A). The intraluminal black specks represent Onyx, and the orange deposits indicate perivascular hemosiderin deposition (Fig. 4B). Post-op angiogram confirmed complete resection of the AVM with no residual (Fig. 6). Furthermore, the patient reported complete resolution of her nausea and was discontinued off antiemetics. The patient tolerated these procedures very well and remained neurologically intact throughout her hospital course.

Discussion

In this report, we present a unique case of Onyx extravasation complicating surgical resection of a residual AVM following embolization. Despite the widespread use of endovascular embolization to treat AVMs, reported cases of Onyx leakage during or following AVM embolization are rare. As per our search, this is the second report of such case in the literature.

Endovascular embolization with Onyx is commonly utilized in the treatment of intracranial AVMs, often in conjunction with radiation or surgical resection. Complications of the procedure are relatively infrequent. In a prospective, multi-institutional study of 117 patients, Pierot et al. [14] reported a morbidity and mortality rate of 5.1% and 4.3%, respectively, comparable to those reported in other studies [5, 18]. Periprocedural complications may include unintended vascular occlusion, vessel perforation, or stuck microcatheters, which may lead to neurologic deficit secondary to ischemic insult or intracranial hemorrhage [8, 22]. While reports of these types of complications have been well documented in the literature, reports of Onyx extravasation are relatively rare. Here, we report a case in which Onyx extravasated from a ruptured left PICA aneurysm, which was seen later intraoperatively during resection of the residual AVM.

Pathologic studies of embolized AVMs have demonstrated varying results with regard to the frequency with which Onyx may extravasate during embolization. In one study investigating histopathologic changes in 32 AVM specimens (16 ruptured) after embolization, Natarajan et al. found no evidence of extravasation of embolic material [11]. However, in a more recent study of 101 AVMs (taken from 96 patients, 39% of whom presented with hemorrhage), extraluminal embolic agent was observed in 40%. The authors note that given the fact that many of these AVMs were removed shortly after the time of embolization, it is possible that some amount of embolic material can extravasate either during embolization or

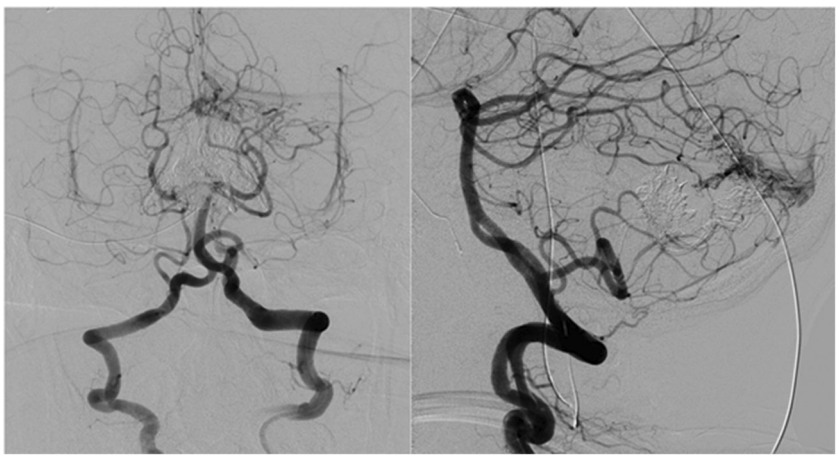

Fig. 3 Post-embolization angiogram, demonstrating complete occlusion of the left PICA aneurysm and 75% obliteration of the vermian AVM

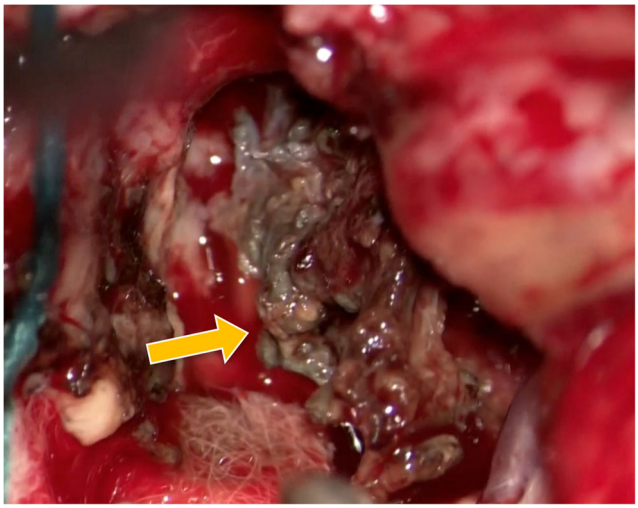

Fig. 4 The Onyx black cast (arrow) observed intraoperatively

soon after secondary to dehiscence of the vessel wall [20]. As we discovered in our case, the presence of extraluminal Onyx may adhere to surrounding tissue, making surgical resection particularly difficult.

Searching the literature, we identified one other case that strongly resembles ours. Therein, a 44-year-old male patient presenting with subarachnoid hemorrhage was found to have a left cerebellar Spetzler-Martin grade 1 AVM associated with a ruptured left PICA aneurysm. Coil embolization was used to treat the ruptured aneurysm, and further embolization and resection of the AVM were planned afterwards. On the patient's second admission, the AVM was embolized with Onyx through the left PICA, and extravasation of Onyx at the nidus was observed. Intraoperatively, while dissecting around the AVM, an Onyx cast was identified and removed [7]. Similar to our case, the patient did not suffer any neurologic deficit as a result of Onyx extravasation.

Multiple factors come into play that may lead to leakage of Onyx during embolization, including viscosity, volume, and injection speed of the embolic material. The viscosity, and more so the volume, of Onyx determine the pressure of injection. Ikeda et al. used Onyx-34 which is more viscous than the Onyx-18 we used in our patient. The ability of Onyx-34 to diffuse is less than Onyx-18, which translates into greater injection pressure and higher chances of leakage. Another parameter to bear in mind is the injection speed. Onyx contains DMSO which can induce vasospasm if injected too quickly which creates resistance to flow and elevates the injection pressure even more. Therefore, slow injection speeds of ≤ 0.1 ml/min are advised to minimize extravasation [2–4, 10, 12]. The definitive cause of extravasation could not be identified in our patient; however, it most likely occurred due to injection into a fragile vessel wall.

In our case, although most of the Onyx leaked into the cerebellar parenchyma, imaging showed a small amount inside the fourth ventricle, which may have contributed to the hydrocephalus developed later. Had the lesion been closer to the surface, more of the embolic material would seep into the subarachnoid space and ventricles. When Onyx comes in contact with water (i.e., in blood plasma or in tissue), it solidifies and becomes adherent to the surrounding tissue, distorting the anatomical plane of dissection which can make resection particularly challenging. Therefore, it is crucial that the surgeon be patient with careful dissection around the entangled neurovasculature with gentle traction in order to maximally resect the Onyx while avoiding injury. Furthermore, Onyx casts are potentially space occupying lesions which can exert a mass effect. In our case, there was no evidence of significant

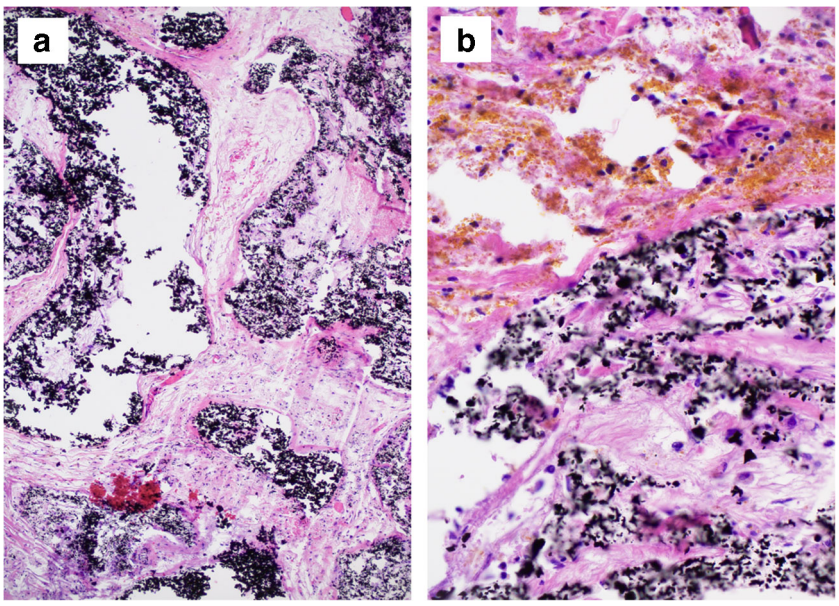

Fig. 5 The lesion is composed of disorganized defective vasculature without capillary connection between arteries and veins with brain parenchyma in the intervening area among the blood vessels. Therapeutic embolization material (black) is noted within the vascular lumen (A, 100x and B, 400x; H&E). Perivascular hemorrhage evidenced by the hemosiderin (bright orange) deposition is present (B, 400x; H&E)

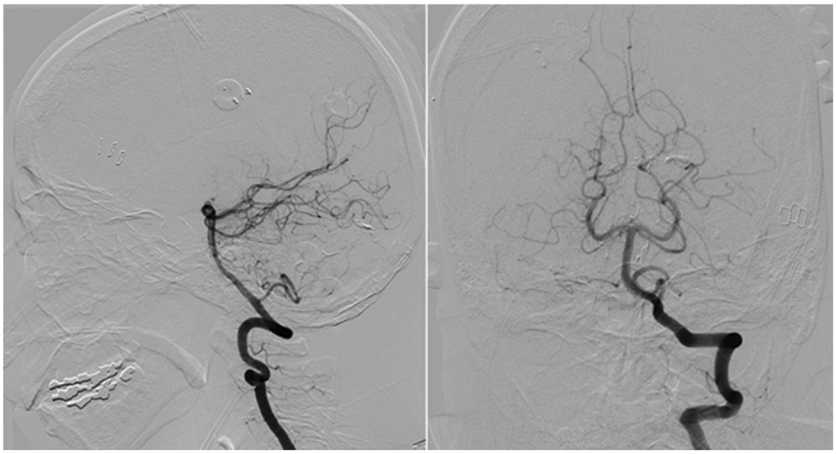

Fig. 6 Post-operative angiogram, demonstrating complete obliteration of the AVM with no residual

mass effect or midline shift; however, this will be detrimental had it occurred in more confined areas like the brainstem.

The more recently developed Onyx HD-500 has increased viscosity that lessens the likelihood of reflux into the parental artery. Its use for embolization of unruptured aneurysms has also gained popularity in recent years, with reported cases of extra-aneurysmal leakage during embolization [15, 16]. In a prospective case series involving 123 aneurysms in 119 patients, Onyx extravasated into the subarachnoid space causing subarachnoid hemorrhage while embolizing a giant internal carotid artery aneurysm [9]. Furthermore, leakage of Onyx has been noted to occur occasionally during preoperative embolization of highly vascular tumors [17]. In one report, Ocak et al. describe a case in which Onyx was discovered overlying part of the cerebellum, brainstem, and trigeminal nerve during resection of a pre-operatively embolized hemangioblastoma [13]. In a case series of extracranial vascular malformations of the head and neck, Arat et al. report a case of subcutaneous extravasation of Onyx, ultimately requiring surgical removal of the Onyx cast [1]. Nonetheless, we have not found any cases in the literature where leaked Onyx was not surgically resected. Although in our patient surgery was indicated for a different purpose (i.e., removal of residual AVM), this still begs the question of whether Onyx leakage can be managed conservatively. Furthermore, following embolization, the patient's symptoms have subsided except for the nausea which persisted despite antiemetics and only resolved after Onyx resection. Although this phenomenon was never reported in previous published cases of Onyx leakage, this raises the question of whether the nausea was caused by possible Onyx-induced neurotoxicity. Onyx can cause a long-standing inflammatory response in embolized AVMs as well as invasion of neuroglial cells [11]. Animal and in vitro experiments have shown DMSO—the main culprit behind potential neurotoxicity—to induce reactive gliosis [25] and disrupt mitochondrial and membrane integrity in cultured neurons [6, 24].

Conclusion

Embolization of ruptured vascular lesions in the setting of acute hemorrhage can be complicated by extravasation of Onyx into the brain parenchyma or subarachnoid space and ventricles. Encountering the adherent Onyx cast intraoperatively may complicate surgical resection, which can present particular intraoperative challenges the neurosurgeon must be prepared for. In our patient, complete excision of the Onyx cast and the AVM was safely achieved. However, whether leaked Onyx can be managed conservatively remains to be determined. Furthermore, the resolution of our patient's nausea after onyxectomy suggests that Onyx might play a role in the pathogenesis of nausea due to its potential neurotoxic effects. This needs to be elucidated by future investigations and case reports.

Patient consent The patient has consented to the submission of the case report for submission to the journal.

References

1. Arat A, Cil B, Vargel I, Turkbey B, Canyigit M, Peynircioglu B, Arat Y (2007) Embolization of high-flow craniofacial vascular malformations with onyx. Am J Neuroradiol 28:1409–1414
2. Ayad M, Eskioglu E, Mericle RA (2006) Onyx®: a unique neuroembolic agent. Expert review of medical devices 3:705–715
3. Chaloupka JC, Huddle DC, Alderman J, Fink S, Hammond R, Vinters HV (1999) A reexamination of the angiotoxicity of superselective injection of DMSO in the swine rete embolization model. Am J Neuroradiol 20:401–410
4. Chaloupka JC, Vinuela F, Vinters HV, Robert J (1994) Technical feasibility and histopathologic studies of ethylene vinyl copolymer (EVAL) using a swine endovascular embolization model. Am J Neuroradiol 15:1107–1115
5. Crowley RW, Ducruet AF, Kalani MYS, Kim LJ, Albuquerque FC, McDougall CG (2015) Neurological morbidity and mortality associated with the endovascular treatment of cerebral arteriovenous malformations before and during the Onyx era. J Neurosurg 122:1492–1497

6. Galvao J, Davis B, Tilley M, Normando E, Duchen MR, Cordeiro MF (2014) Unexpected low-dose toxicity of the universal solvent DMSO. FASEB J 28:1317–1330
7. Ikeda H, Imamura H, Agawa Y, Imai Y, Tani S, Adachi H, Ishikawa T, Mineharu Y, Sakai N (2017) Onyx extravasation during embolization of a brain arteriovenous malformation. Interv Neuroradiol 23:200–205
8. Loh Y, Duckwiler GR (2010) A prospective, multicenter, randomized trial of the Onyx liquid embolic system and N-butyl cyanoacrylate embolization of cerebral arteriovenous malformations. J Neurosurg 113:733–741
9. Molyneux AJ, Cekirge S, Saatci I, Gál G (2004) Cerebral aneurysm multicenter European Onyx (CAMEO) trial: results of a prospective observational study in 20 European centers. Am J Neuroradiol 25: 39–51
10. Murayama Y, Viñuela F, Ulhoa A, Akiba Y, Duckwiler GR, Gobin YP, Vinters HV, Greff RJ (1998) Nonadhesive liquid embolic agent for cerebral arteriovenous malformations: preliminary histopathological studies in swine rete mirabile. Neurosurgery 43:1164–1172
11. Natarajan SK, Born D, Ghodke B, Britz GW, Sekhar LN (2009) Histopathological changes in brain arteriovenous malformations after embolization using Onyx or N-butyl cyanoacrylate. J Neurosurg 111:105–113
12. Natarajan SK, Ghodke B, Britz GW, Born DE, Sekhar LN (2008) Multimodality treatment of brain arteriovenous malformations with microsurgery after embolization with onyx: single-center experience and technical nuances. Neurosurgery 62:1213–1226
13. Ocak PE, Başkaya MK (2018) A rare complication of endovascular embolization: extruded Onyx on trigeminal nerve. Journal of Neurological Surgery Part B: Skull Base 79:S422–S423
14. Pierot L, Cognard C, Herbreteau D, Fransen H, van Rooij W, Boccardi E, Beltramello A, Sourour N, Kupcs K, Biondi A (2013) Endovascular treatment of brain arteriovenous malformations using a liquid embolic agent: results of a prospective, multicentre study (BRAVO). Eur Radiol 23:2838–2845
15. Rahme R, Grande A, Jimenez L, Abruzzo TA, Ringer AJ (2014) Onyx HD-500 embolization of intracranial aneurysms: modified technique using continuous balloon inflation under conscious sedation. J Clin Neurosci 21:1383–1387
16. Rahme R, Grande A, Jimenez L, Abruzzo TA, Ringer AJ (2014) Predicting parent vessel patency and treatment durability: a proposed grading scheme for the immediate angiographic results following Onyx HD-500 embolization of intracranial aneurysms. Journal of neurointerventional surgery 6:754–760
17. Rangel-Castilla L, Shah AH, Klucznik RP, Diaz OM (2014) Preoperative Onyx embolization of hypervascular head, neck, and spinal tumors. Experience with 100 consecutive cases from a single tertiary center. Journal of neurointerventional surgery 6:51–56
18. Saatci I, Geyik S, Yavuz K, Cekirge HS (2011) Endovascular treatment of brain arteriovenous malformations with prolonged intranidal Onyx injection technique: long-term results in 350 consecutive patients with completed endovascular treatment course. J Neurosurg 115:78–88
19. Szajner M, Roman T, Markowicz J, Szczerbo-Trojanowska M (2013) Onyx® in endovascular treatment of cerebral arteriovenous malformations–a review. Pol J Radiol 78:35
20. Tailor C, Ashby WS, Gorassini DR, Lownie SP, Walsh K, Pelz D, Hammond RR (2019) Embolized cerebral arteriovenous malformations: a multivariate analysis of 101 excised specimens. J Neurosurg 1:1–7
21. Terada T, Nakamura Y, Nakai K, Tsuura M, Nishiguchi T, Hayashi S, Kido T, Taki W, Iwata H, Komai N (1991) Embolization of arteriovenous malformations with peripheral aneurysms using ethylene vinyl alcohol copolymer: report of three cases. J Neurosurg 75:655–660
22. Weber W, Kis B, Siekmann R, Kuehne D (2007) Endovascular treatment of intracranial arteriovenous malformations with onyx: technical aspects. Am J Neuroradiol 28:371–377
23. Yamashita K, Taki W, Iwata H, Nakahara I, Nishi S, Sadato A, Matsumoto K, Kikuchi H (1994) Characteristics of ethylene vinyl alcohol copolymer (EVAL) mixtures. Am J Neuroradiol 15:1103–1105
24. Yuan C, Gao J, Guo J, Bai L, Marshall C, Cai Z, Wang L, Xiao M (2014) Dimethyl sulfoxide damages mitochondrial integrity and membrane potential in cultured astrocytes. PLoS One 9:e107447
25. Zhang C, Deng Y, Dai H, Zhou W, Tian J, Bing G, Zhao L (2017) Effects of dimethyl sulfoxide on the morphology and viability of primary cultured neurons and astrocytes. Brain Res Bull 128:34–39