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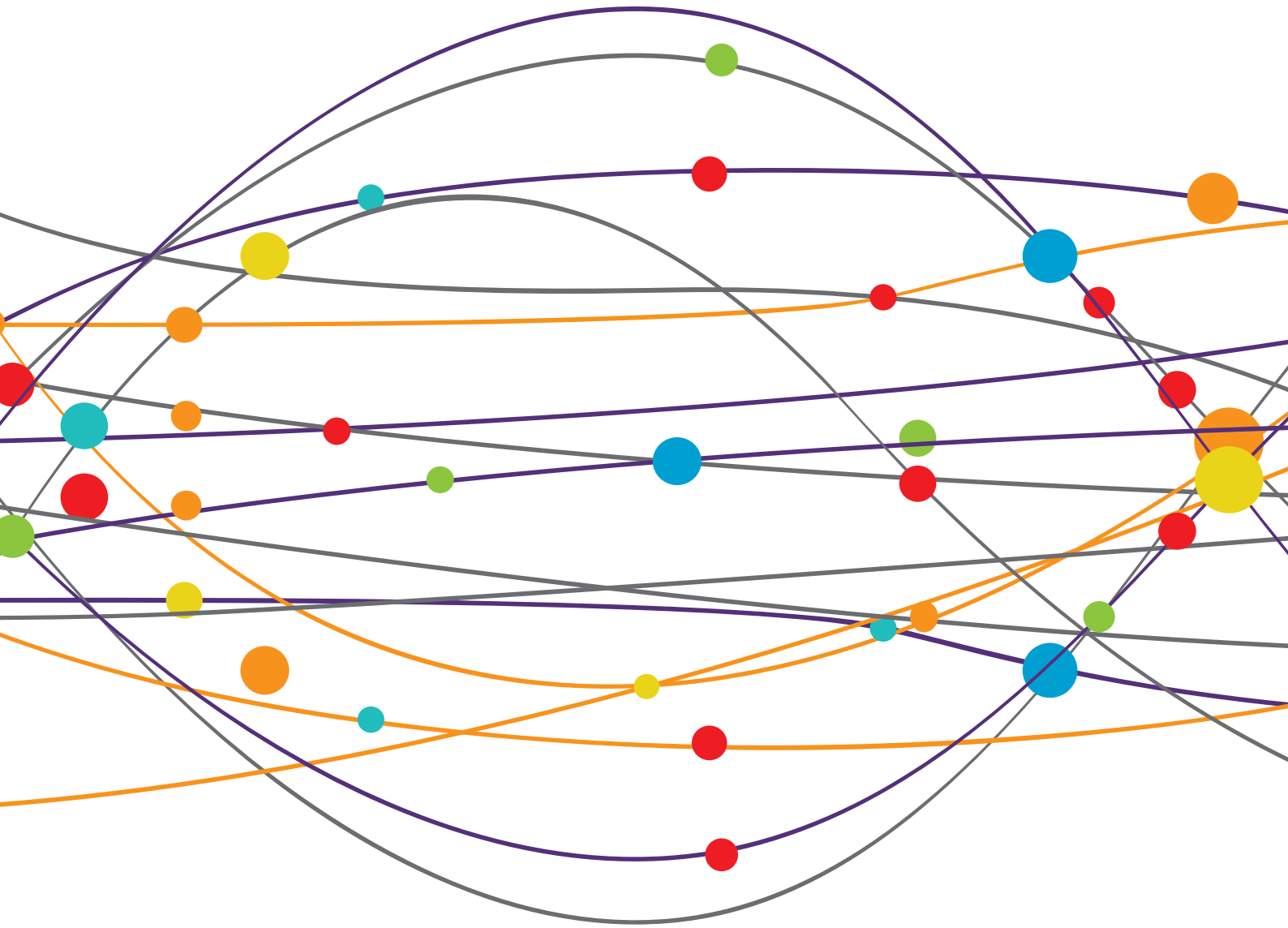

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ENDOVASCULAR AND INTERVENTIONAL NEUROLOGY - CASE REPORT COLLECTION 2021

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CASE REPORT
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Intracranial Subarachnoid Haemorrhage Caused by Cervical Spinal Dural Arteriovenous Fistulas: Case Report

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Cervical spinal vascular abnormalities commonly present with progressive myelopathy as a result of venous congestion. They are not very prone to bleed and tend to be underdiagnosed due to their subtle clinical presentation. We came across a rare case of intracranial subarachnoid haemorrhage caused by cervical spinal dural fistula in the Imperial College Healthcare NHS Trust Hospitals/UK in June 2020. We diagnosed the patient under strict evidence base medicine guidance, which otherwise would have been missed. We discussed the case in several multidisciplinary team (MDT) meetings, and patient was treated under the joint care of the neurology and neurosurgical teams. Patient made a full recovery and discharged home with no neurological defects or complications. Here, we reported this case with all the evidence we gathered from our MDT discussion. We hope our experience would help improve the diagnosis and management protocol for future patients with a similar condition.

Keywords: subarachnoid haemorrhage, spinal dural arteriovenous fistula, interventional neuroradiology, indocyanine green angiography, neurosurgery

INTRODUCTION

Although ruptured cerebral aneurysms cause most spontaneous subarachnoid haemorrhages (SAHs), they can also result from various rare conditions in about 5–10% of patients (1). Approximately 1% of reported intracranial SAHs are related to spinal pathologies, such as arteriovenous lesions (2).

Cervical arteriovenous fistulas (AVFs) are rare vascular malformations found in 1–2% of patients with spinal AVFs. Typically, AVF symptoms are associated with venous congestion, which can include subtle, slow-onset paraparesis (40%), back pain or radiculopathy (28%), and sphincter disturbances that are exacerbated by activity (3).

Intracranial SAHs caused by spine vascular abnormalities are extremely rare. In a literature search, only five studies were found published in the past decade (3–7).

Here, we discuss a case of intracranial SAHs caused by cervical AVF, focusing on how we came to the diagnosis under strict evidence guidance and treatment plans made under several multidisciplinary team (MDT) discussions.

CASE PRESENTATION

A 40-year-old female attended the hospital with a brief episode of chest tightness radiating toward her back, immediately followed by severe headache, neck stiffness, nausea and vomiting, and photophobia. She was previously fit and well with no past medical history and no history of trauma. She was not on any anticoagulation therapy and had no significant family history of cancer or neurological disorder.

On examination, she demonstrated neck stiffness and occipital tenderness. There were no other positive findings in her initial neurological examinations. Her Glasgow Coma Scale (GCS) was 15, her mental state and speech were normal, her cranial nerves were unaffected and she had good power on all four limbs and a normal gait.

A head CT was performed on arrival (level I evidence), which showed acute subarachnoid blood predominantly perimesencephalic in distribution with extension into the ventricular system (**Figure 1**). A CT angiography (CTA) intracranial and a cerebral digital subtraction angiography (DSA) was arranged within 24 h of admission (level I evidence) (8); both showed no convincing evidence of intracranial aneurysm or other vascular abnormalities.

The patient was subsequently closely managed under the joint care of neurology and neurosurgery. She was being monitored for signs of hydrocephalus and vasospasm during the acute stage (level I evidence). Her case was discussed in the first neuro-radiology MDT and was recommended for baseline MRI/MR angiography (MRA) 1 week into her SAH (level I evidence). The MRI/MRA result showed normal brain parenchyma and no evidence of an intracranial vascular malformation or aneurysm. However, there was a find of a small rounded lesion with enhancement at the level of C2–3, anterior to the cervical cord (**Figure 2**, left panels). This is consistent with an arteriovenous malformation (AVM)/AVF. A spinal DSA was organised, which showed a dural AVF situated at the ventral aspect of the cervical spine at the level of C2–3. Two radicular branches were coming off the left vertebral artery (VA) at the same level, travelling deep into the spinal canal and feed into the dural AVF. No anterior spinal artery (ASA) involvement was noted. It was a small 3–4-mm dilated varix in the midline and ventral to the cervical spinal cord, likely on the venous side, which is likely to represent the site of a recent haemorrhage (**Figure 2**, middle and right panels).

Her case was further discussed during the second neuroradiology MDT meeting, which included a neurologist, an interventional neuro-radiologist and neurosurgeons. Given that the two feeding branches are too small to navigate the micro-catheter, it was deemed unsuitable for endovascular treatment (level V evidence). Disconnection of dural AVF (level IV evidence) with intraoperative indocyanine green (ICG) angiogram guidance (level I evidence) was recommended by senior consultant neurosurgeons (9). The MDT decided to offer this patient surgery.

The patient fully consented and agreed to have surgery. Following surgery, she was neurologically well but complained of severe head and neck pain that had not improved since onset and very poor neck stiffness. Her pain was not controlled by regular paracetamol, codeine and morphine. Our pain team recommenced a ketamine trial (level I evidence), to which she responded well. Her headache dropped from a rating of 10/10–2/10 ∼15 min after 25 mg of ketamine was administered. She subsequently commenced a 6-day course of ketamine 25 mg every 4 h for pain control, which was replaced with pregabalin 75 mg twice a day afterwards. Our physical therapist/occupational therapist (PT/OT) reviewed her neck stiffness and concluded that it was mainly due to subsequent fear of harming and avoiding activity/guarding of movement, which is fairly common in patients after spinal surgeries. They provided information for self-managing exercise and provided her with information on how to adapt movement to limit the pain and encourage a gradual return to normal activity (level II evidence). Other than physical symptoms, the patient had been very anxious during her postoperative recovery, mainly with the restrictions on inpatient management and no visitor rules due to COVID-19 restrictions. All patients found it difficult due to the lack of family support during this period. Our specialty nurse used iPads to arrange for family calls to ensure she has proper access to her loved ones, which helped calm her down and involve the family in her care.

With her treatment completed and symptoms fully controlled, she was discharged home from the hospital on the 10th postoperative day. The PT/OT had arranged for ongoing support from the community. Outpatient follow-up used virtual stream 6 weeks after discharge. The patient was well, was no longer using painkillers and had returned to her normal lifestyle.

It was planned for her to receive a follow-up angio-spinal 6 months post operation per our neurovascular MDT recommendation. However, the procedure was delayed due to the COVID-19 restrictions. She eventually had follow-up spinal DSA 10 months post-surgery. The result showed that the C2–3 no longer demonstrated dural AVF, and no further arteriovenous shunting presented (**Figure 3**).

Figure 4 summarises the timeline for this case.

DISCUSSION

Spinal Dural Arteriovenous Fistulas: What Do We Know About Them?

A literature review suggested that, in most cases, spinal dural AVF presented with gradual onset myelopathy as venous drainage gradually fails. However, there are few documented cases of acute haemorrhages. They were all found by MRI and MRA of the whole spine when investigating non-aneurysmal SAH (NASAH). The mechanism by which the spinal bleeds cause the intracranial SAH is unclear. Typically, there is initially an intracranial SAH that then spread down to the spine. The result of intracranial SAH from the spinal lesion is most likely a reverse form of spreading from the typical scenario, consistent with blood pattern at foremen magnum. For intracranial AVMs, the Spetzler Martin Grading Scale was applied by evaluating AVM size, the pattern of venous drainage and eloquence of brain location to estimate the risk of surgery (10). However, for spinal AVM/AVFs, the

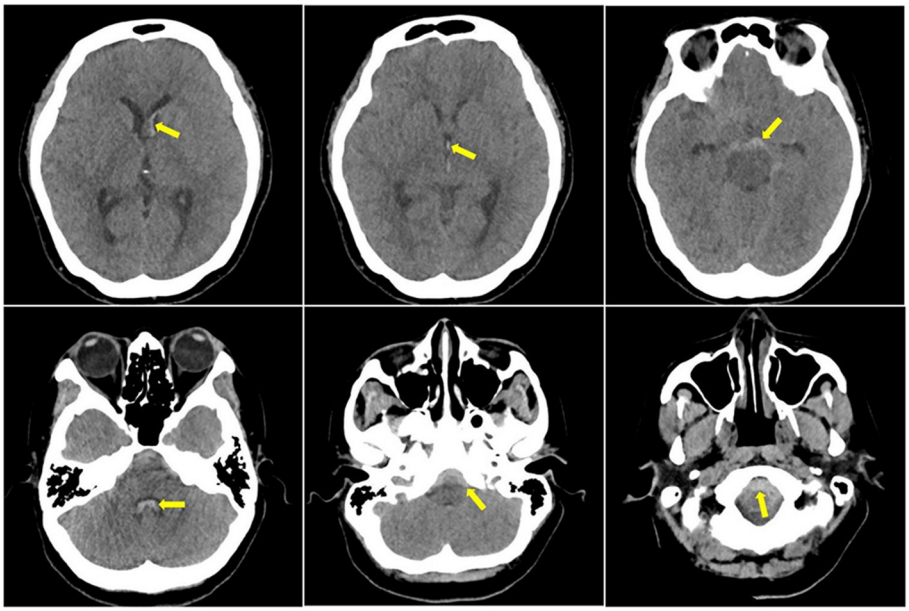

FIGURE 1 | Initial CT head showed subarachnoid haemorrhage (SAH) present in the frontal horn of the left lateral ventricle, third ventricle and fourth ventricle, and the foramen magnum; yellow arrows indicate blood component in the scans.

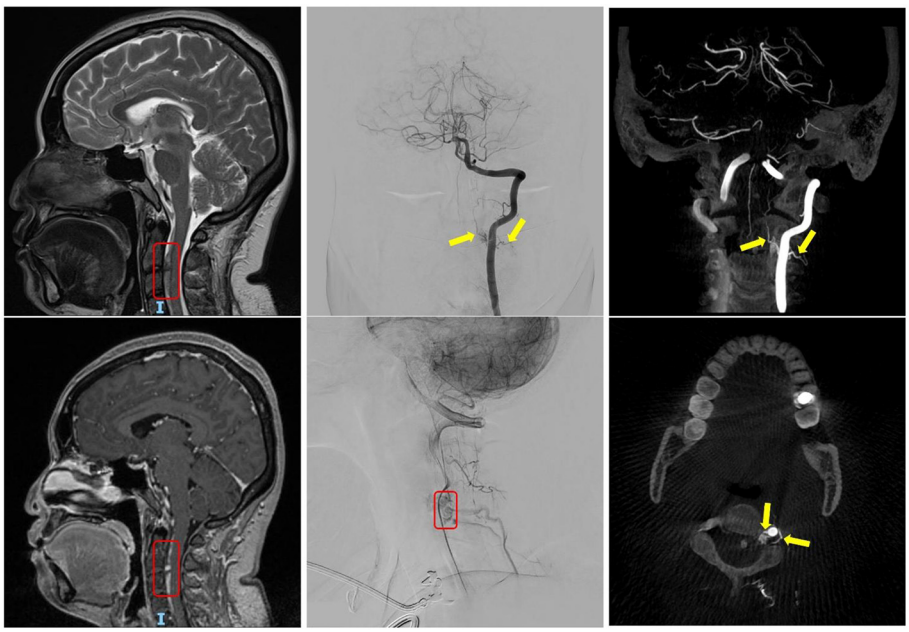

FIGURE 2 | The left panels show the finding of the C2–3 dural arteriovenous fistula (AVF) in routine MRI head, highlighted within the red box. The middle and right panels show the digital subtraction angiography (DSA) cervical spine and the angio-CT of L-VA. The yellow arrows indicate the two supplying arteries; and the red boxes indicate tortuous venous drainage of the AVF.

classification system is not as straightforward. Historically, there had been three different systems of classifications.

The very first classification system was created between 1991 and 1998 by the combined efforts of different authors. The system describes four different types, as follows: type I, a single coiled vessel (spinal dural AVF); type II, intramedullary glomus AVM; type III, juvenile vessels; and type IV, intradural perimedullary (AVF). Different from the chronic presentation of most spinal AVMs or AVFs, type IV mostly presents acutely with more progressive myelopathy. Djindjian et al. (11) and Heros et al.

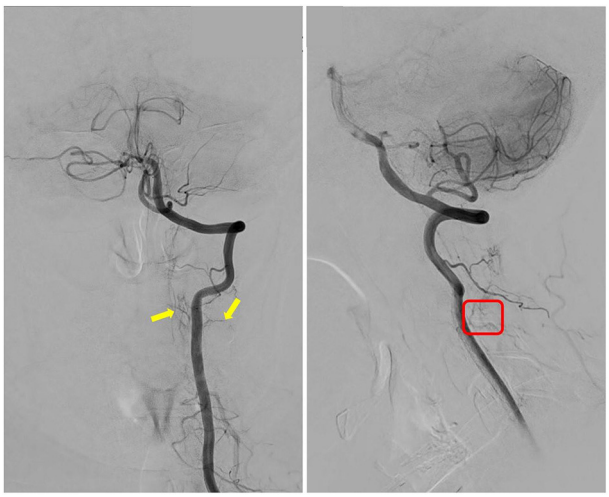

FIGURE 3 | Follow-up spinal digital subtraction angiography (DSA) demonstrated images of L-VA; the yellow arrows indicate that the two supplying arteries no longer feed into the arteriovenous fistula (AVF); and red box indicates that tortuous venous drainage of the AVF had disappeared as compared with pre-op DSA image.

(12) suggested further dividing type IV spinal AVF into three subtypes: subtype I, single arterial supply (ASA), single small fistula, slow ascending perimedullary venous drainage; subtype II, multiple arterial supplies [ASA and posterior spinal artery (PSA)], multiple medium fistulae, slow ascending perimedullary venous drainage; and subtype III, multiple arterial supplies (ASA and PSA), single giant fistula, large ectatic venous drainage.

Kim and Spetzler (13) in a review in 2006, proposed a modified classification system for spinal arteriovenous lesions based on specific anatomical and pathophysiological factors. The different types are described in the following: (1) extradural AVF, (2) intradural dorsal AVF, (3) intradural ventral AVF, (4) extra-intradural AVM, (5) intramedullary AVM, and (6) conus medullaris AVM.

Most recently in 2019, Lenck et al. (14) suggested the Toronto Classification of AVM/AVF of spine based on the anatomic feature and the topography of the shunting site. Under this system, the spinal vascular lesions were divided into the following: (a) spinal cord AVM—glomus intramedullary lesions; (b) pial AVF—shunts located superficial to the cord in the subpial space; (c) dural AVF—lesion located intradural but extrapial; (d) epidural AVF—lesions located outside dura but within the spinal canal; (e) paraspinal AVF—lesion pushing through to the outside of spinal canal and drain into para spinal venous plexuses; and (f) spinal arteriovenous metameric syndrome (SAMS)—lesions that involve multiple tissue layers (e.g., spinal cord, bone, paraspinal musculature, subcutaneous tissues, and skin) in one or several metameric segments.

Comparing among the three systems, our case here fitted mostly under the Toronto Classification as a type c dural AVF, as it had two radicular branches from L-VA that entered the dura and supply into a large ectatic venous drainage at the C2–3 level.

A schematic image of the lesion is shown in **Figure 5**.

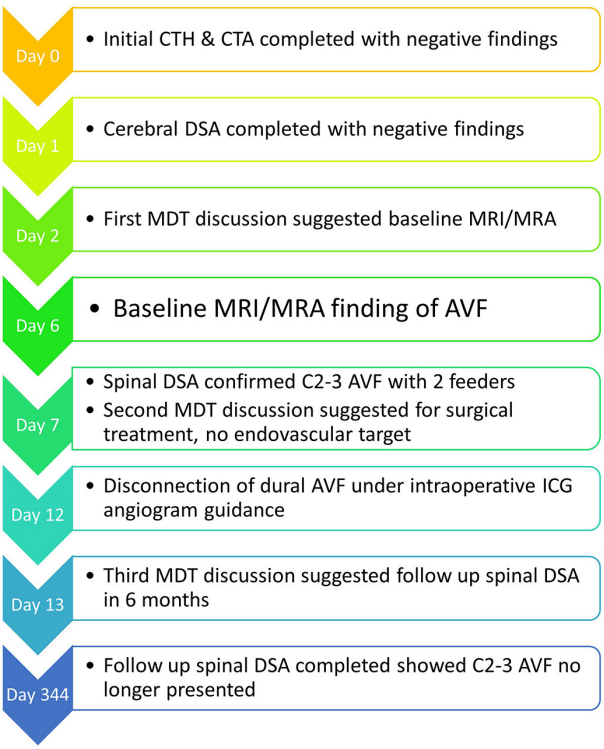

FIGURE 4 | A diagram of timeline for this case.

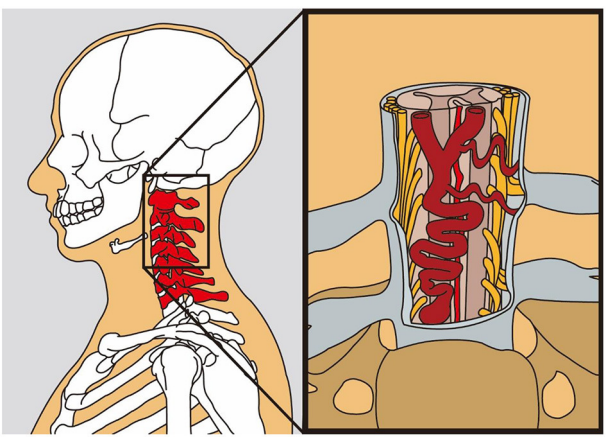

FIGURE 5 | The schematic model of the dural arteriovenous fistula (AVF) lying in the ventral aspect of the cervical spinal cord (this figure is an artwork produced by Mr. Huang for us; he had kindly permitted us to publish his work in our manuscript).

Diagnosis Pathway: Routine Spinal Imagining?

Up to 10% of all spontaneous SAH are NASAHs. The evaluation of SAH patients with negative DSA is sometimes a diagnostic challenge. Kashefiolasl et al. studied 103 NASAH patients. Among them, 23 (22%) patients had a CT negative SAH, diagnosed by positive LP. All patients received an MRI of the

spine; only two (1.9%) patients presented with a positive finding. Both patients complained of radicular sciatic pain. The detection rate increased by up to 25% in cases where patients with radicular sciatic pain at the presentation of symptoms received an MRI. The study concluded that routine radiological investigation of the spine in every NASAH patient is not recommended due to the rarity of the pathology and should be done as symptom orientated (7). Similar findings were also noted in five other studies investigating NASAH *via* MRI spine to locate the source of bleeding; they report only a 1% positive finding (15).

In our case, the patient was initially being treated as a NASAH, and the lesion was picked up during the routine follow-up MRI/MRA. If the lesion level was two vertebrae lower, the diagnosis of such a bleeding lesion would not have been found. In our literature research, within the past decade, there had been one case study describing intracranial SAH caused by a thoracic spinal vascular lesion (15). It was discussed with our neuro-radiologist if routine spinal imaging would be warranted for other NASAHs. It was concluded that given the history in our case that she did have one episode of chest tightness, radiating toward her back immediately prior to the headache, a full spine MRI was clinically warranted even if the baseline MRI/MRA head and neck was negative (level IV evidence). However, running routine spinal scans for all NASAH is still not recommended due to the rarity of the condition.

Treatment Options

Limited resources are reporting the treatment options of spinal AVMs/AVFs. Hiramatsu et al. (3) reported the treatment outcome from a 59-patient cohort. Of the 59 lesions, 28 (47%) were treated with direct surgery only, and eight (14%) were managed conservatively. Fifteen lesions (25%) were treated with endovascular embolisation only. Eight lesions (14%) were treated with direct surgery and endovascular embolisation (3, 16–18). Unfortunately, no publications have presented and discussed follow-ups and the treatment outcome for those cohorts.

Following a discussion in our neurovascular MDT, the patient's lesion was deemed unsuitable for endovascular embolisation (level V evidence). The final decision was to offer her C2–3 posterior laminectomy and disconnection of dural AVF (level IV evidence). She was made aware of her condition, the rationale for this treatment option, and the risks and benefits associated with it. She made the informed decision of proceeding with the treatment.

CONCLUSION

We diagnosed and treated a rare case of intracranial SAH secondary to cervical dural AVF guided by evidence-based medicine. Intracranial SAH caused by cervical spine vascular abnormalities is rare; however, in the event of such a case, it is essential to look for any spinal symptoms in NASAH. A full spinal MRI is clinically warranted for any NASAH patients presenting with transient or persistent spinal symptoms (level IV evidence).

Our patient recovered well after surgery under the joint care of our specialist nursing staff, neurologists, neurosurgeons, pain team, and rehabilitation therapists. The management of her case had again emphasised that collaboration of MDT is critical for patient recovery and could affect the overall experience for the patient (level I evidence).

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JZ performed the neurological examination, wrote the first draft of the article and was responsible for the overall content. NR evaluated the radiological images and contributed mainly to the discussion of the cases. RN performed the surgical treatment on the patient and contributed significantly to the patient's discussion and revision of the first draft. All authors reviewed and approved the final manuscript and ensured that all the questions regarding the accuracy of the article were appropriately investigated and resolved.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.685332/full#supplementary-material

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CASE REPORT
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Case Report: Double Micro-Guidewire Technique for Emergent Rescue of Proximal Stent Collapse During Recanalization of Nonacute Occlusion of Vertebral Artery

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Cerebral arteries are usually tortuous, and in the treatment of cerebrovascular diseases with stenting, a stent deployed may be collapsed at one end, leading to reduced blood flow and subsequent stent occlusion. Immediate rescuing measures should be implemented to prevent severe ischemic events. In this case report, we present a case with V4 segment occlusion of the right vertebral artery treated with endovascular stent angioplasty. An Enterprise stent deployed at the occlusion segment was collapsed at the proximal end after withdrawal of the delivery system. Immediate rescuing measures were taken by navigating a micro-guidewire through the lateral stent mesh at the proximal end into the stent lumen followed by advancing a second micro-guidewire right through the reopened proximal stent end into the stent lumen for deployment of a supporting balloon-expandable Apollo stent to prevent stent collapse. Follow-up digital subtraction angiography 6 months later demonstrated patent stents and unobstructed blood flow.

Keywords: cerebrovascular disease, atherosclerotic occlusion, stent collapse, complications, double micro-guidewires

INTRODUCTION

As a major health burden worldwide, strokes result in a high rate of morbidity and mortality (1, 2). Intracranial atherosclerosis accounts for ∼5–10% of all strokes and transient ischemic attacks in the world (1), whereas in Asia, intracranial atherosclerotic stenosis is responsible for 33–37% of acute ischemic strokes (3). It is demonstrated that symptomatic nonacute large intracranial arterial atherosclerotic occlusion is an independent factor to predict poor outcomes, recurrent strokes, and major stroke problems across the world (4, 5). A large number of patients with chronic large intracranial artery occlusion continue to be symptomatic in spite of maximal medication treatment (6), and these symptomatic patients with chronic hemodynamic impair are at a high risk of future strokes (4). Even though no consensus exists on the best therapeutic approaches of nonacute large intracranial artery occlusion, endovascular recanalization with angioplasty alone or with stent angioplasty is feasible, safe, and efficacious in highly selected patients with improved clinical

outcomes after treatment (7–10). Based on computed tomography (CT) imaging, CT perfusion, magnetic resonance imaging (MRI), and clinical symptoms, the indications for endovascular recanalization are reported to be chronic occlusion of large intracranial arteries; recurrent ischemic neurological deficits (TIA or stroke); or progressive neurologic impairment symptoms, cerebral border zone infarction, and/or a decrease in cerebral blood flow and presence of a vascular bed at the distal end of the occlusion with the diameter of the occluded vessel exceeding 2 mm and the length being <15 mm. In the treatment of intracranial atherosclerotic stenoses, percutaneous angioplasty and stenting have significantly reduced the incidence of ischemic stroke, which has played an increasingly important role in neurology (11, 12). However, when a stent is deployed for the treatment of atherosclerotic stenoses or chronic occlusion of a tortuous artery, the stent struts at the proximal end may get in close contact or occlude after withdrawal of the inner micro-guidewire due to arterial tortuosity and stenoses, resulting in failure of endovascular devices to pass through the stent and even complete occlusion of the stented artery. In this case, acute revascularization of the occluded stent is necessary to guarantee unobstructed blood flow through the stent and prevent thrombosis or complete occlusion of the stented artery. We have encountered a case with occlusion of the V4 segment of the right vertebral artery, which was treated with deployment of a stent. The stent proximal struts got in close contact and occluded after the delivery system was withdrawn. Acute rescue management was successfully performed by using two micro-guidewires through the stent to deploy a support stent to open the collapsed stent struts.

CASE REPORT

A male patient in his 50s had dizziness for 12 days that was not relieved after administration of medications. He had a history of smoking for 20 years with an average of six cigarettes per day and alcohol abuse for 30 years. Physical examination demonstrated blood pressure 123/78 mmHg, clear consciousness, slightly bad spirits, and no abnormality in the cranial nerve. Muscle strength and tension of limbs were normal. Auxiliary examination showed nothing abnormal in the electrocardiogram or laboratory tests (blood and urine routine, biochemical series, and coagulation items). MRI, MR angiography (MRA), and CT angiography (CTA) revealed occlusion of the right vertebral artery at the V4 segment (**Figure 1A**), which was confirmed by diagnostic digital subtraction angiography (DSA). The patient did not have a family history or genetic information of cerebral infarction or any previous endovascular treatment. Because medication did not perform well, the ischemic symptoms might be further aggravated, resulting in cerebral infarction and even death. To prevent aggravation of this condition, endovascular treatment was performed with written informed consent from the patient. The procedure was conducted under general anesthesia after administration of dual antiplatelet therapy with aspirin (100 mg/d) and clopidogrel (75 mg/d) for 3 days. The Seldinger technique was applied to gain percutaneous access to the femoral artery before insertion of a 6F introducer sheath, and heparin (70 U/kg) was administered intravenously to achieve an activated coagulation time of 150–200 s. DSA was performed to show the anatomy of the occluded artery, and a 300-cm Traxcess micro-guidewire (0.014 inch, Medtronic Inc., Minneapolis, MI, USA) was used to explore and navigate through the occluded segment before being put at the distal P1 segment of one posterior cerebral artery (PCA). Then, an Echelon 10 microcatheter (Medtronic) was sent along the micro-guidewire across the occluded segment to the same distal P1 segment of PCA, and gentle angiography through the microcatheter was performed to demonstrate the vascular structures. An angioplasty balloon catheter (Gateway, Boston Scientific, Natick, Massachusetts, USA) was advanced over the microwire, centered across the lesion, and inflated slowly for angioplasty (2.0 × 13 mm balloon) before an Enterprise stent (4.5 × 28 mm) was deployed at the occluded segment after accurate positioning (**Figures 1B–D**). At the time of stent deployment, the vertebral artery was straightened and smooth (**Figure 1C**), and the proximal end of the stent was wide open with the proximal markers of the stent being spread out (**Figure 1D**). Once the micro-guidewire and the conveying microcatheter were withdrawn, the stent proximal end was collapsed because of compression of the wall of the curved artery, which was exhibited by the closed proximal markers in close contact (**Figures 2A,B**). We tried to navigate a microcatheter (Excelsior SL-10, Stryker Neurovascular, Fremont, California, USA) into the proximal end of the stent, but this was unsuccessful. Then, the 300-cm micro-guidewire was navigated to the stent proximal end and passed through the proximal lateral mesh of the stent (**Figure 2C**). Once the micro-guidewire was sent to the distal segment of the basilar artery, the vertebral artery was straightened, and the stent proximal end was opened with the proximal markers being spread out again (**Figures 2D,E**). Then, a second 200-cm Synchro micro-guidewire was navigated right through the stent proximal end into the real lumen of the stent and sent to the distal segment of basilar artery (**Figures 2F**, **3A,B**). After the 300-cm micro-guidewire was withdrawn, an Apollo 2.5 × 10 mm balloon-expanded stent (MicroPort Medical, Shanghai, China) was navigated along the Synchro micro-guidewire to overlap partially with the proximal segment of the Enterprise stent and was expanded with 4 atm pressure to support the proximal end of the first stent (**Figures 4A–C**). Angiography revealed good apposition of the two stents against the arterial wall with unobstructed blood flow through the stents and improved blood flow in the distal segment. Then, the micro-guidewire and microcatheter were withdrawn. Postoperative vertebral angiography showed complete recanalization of the occluded arterial segment (**Figures 4B,C**), and the Thrombolysis in Cerebral Infarction blood flow was grade 3. DynaCT scan revealed partially overlapped stents (**Figure 4D**). After stenting, both stents were well-patent with favorable forward flow (**Figures 4E,F**). At follow-up 6 months later, head CT showed no obvious abnormality, and physical examination revealed nothing abnormal in the cranial nerve. DSA demonstrated patent stents and unobstructed blood flow through the stents (**Figure 5**).

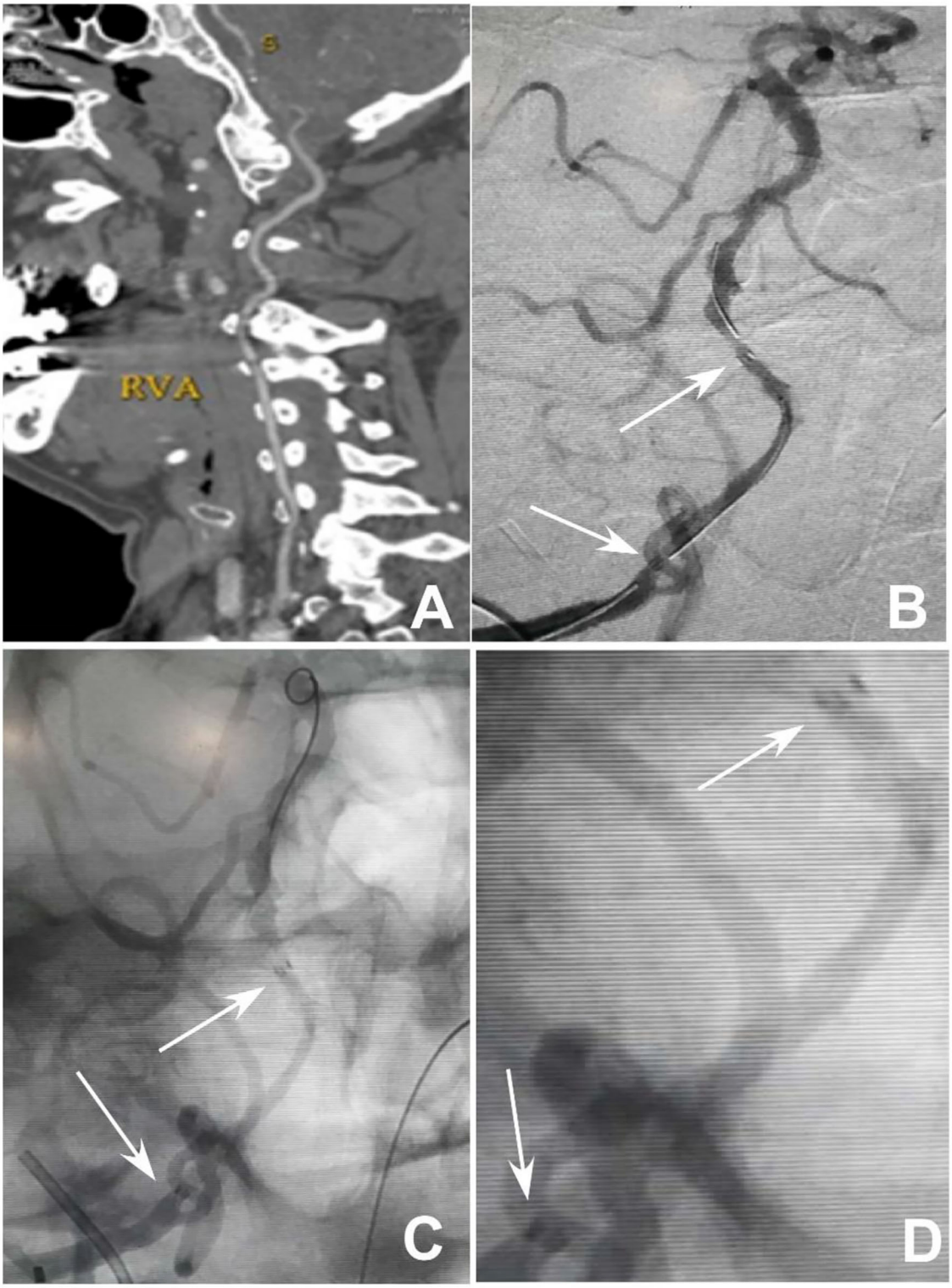

FIGURE 1 | Endovascular treatment of V4 segment occlusion of the right vertebral artery. **(A)** Computed tomography angiography revealed occlusion of the V4 segment of the right vertebral artery without calcification of the occluded artery. **(B)** After balloon expansion of the occluded segment, an Enterprise stent was deployed at the occluded segment. **(C,D)** After deployment of the stent with the micro-guidewire still in the artery, the proximal and distal markers of the stent were spread out with patency of the stent. **(D)** is the local enlargement of **(C)** between the proximal and distal markers of the stent. Arrows indicate the proximal and distal markers of the stent.

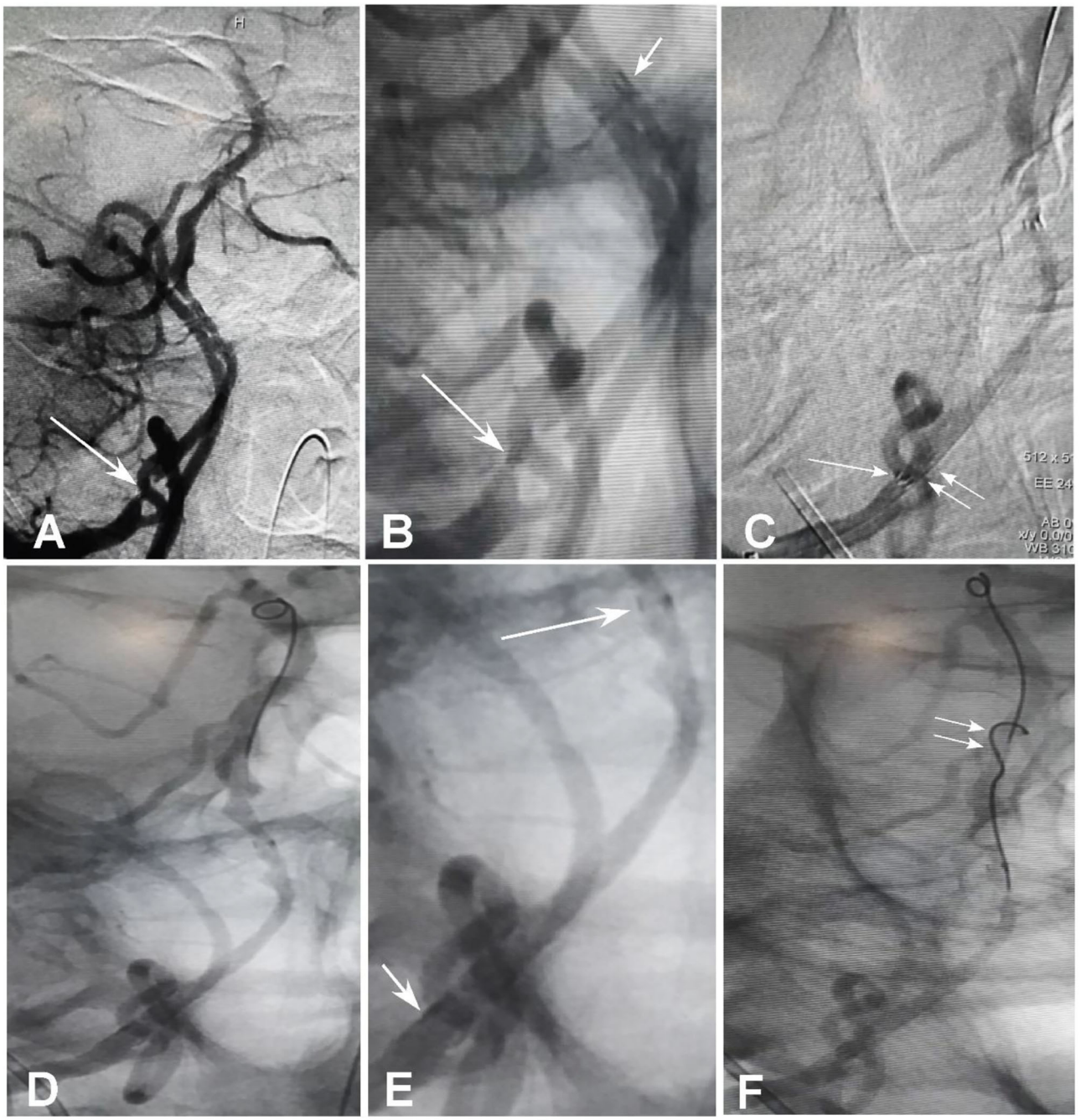

FIGURE 2 | Collapse of the stent proximal end and management. **(A,B)** Withdrawal of the micro-guidewire and microcatheter led to collapse of the stent proximal end with the stent proximal markers in close contact, and the blood flow was reduced through the proximal end. The longer arrow indicates the proximal markers and the shorter arrow the distal markers. **(C)** A 300-cm micro-guidewire was navigated into the stent lumen through the proximal lateral stent mesh rather than through the proximal stent end. The longer arrow indicates the collapsed proximal markers of the stent, whereas the double arrows indicate the micro-guidewire through the stent lateral mesh. **(D,E)** After the micro-guidewire was sent to the distal segment of the basilar artery, the proximal stent end was opened with the proximal markers being spread out [**(E)**, shorter arrow]. The longer arrow indicates the distal stent markers. **(E)** is the local enlargement of **(D)** between the proximal and distal markers of stent. **(F)** A second 200-cm micro-guidewire was sent right through the opened proximal stent end into the stent lumen (double arrows).

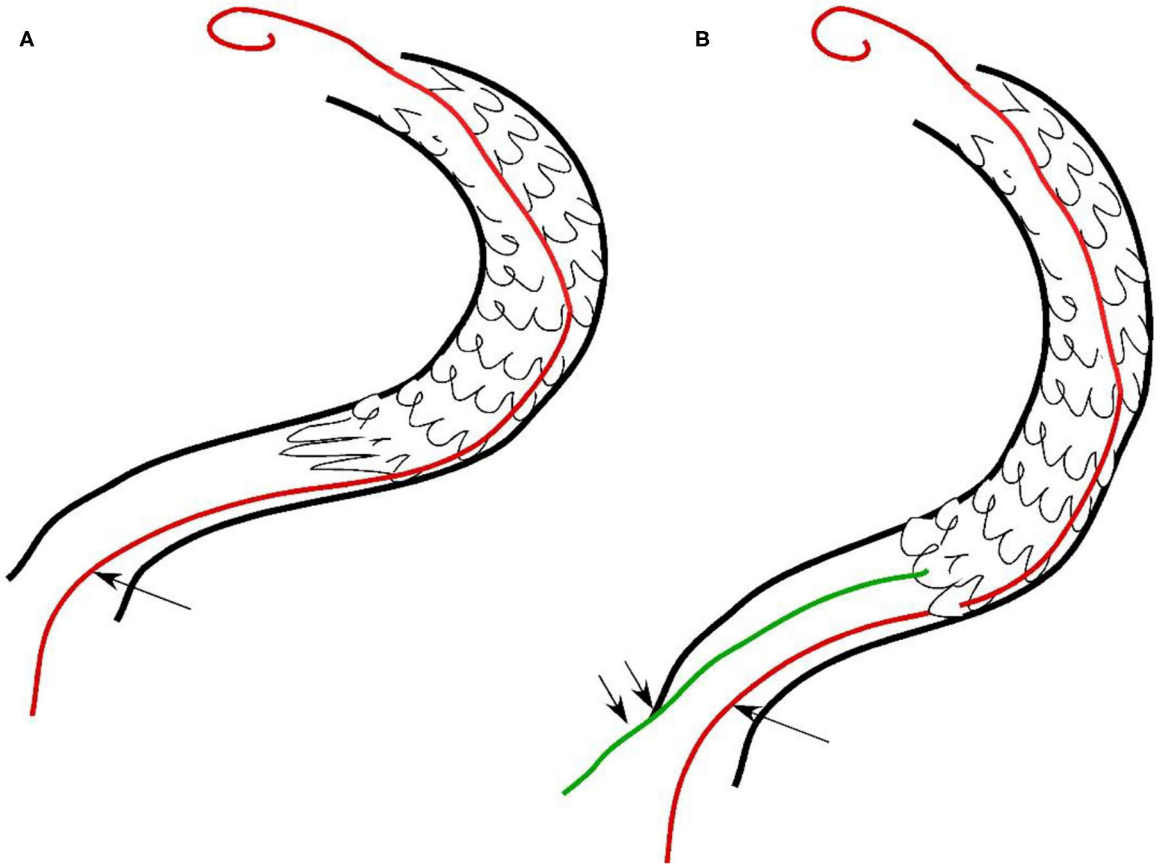

FIGURE 3 | Hand sketch to show the deployment of two micro-guidewires. **(A)** The first micro-guidewire (longer arrow) was sent through the lateral stent mesh into the stent lumen after collapse of the stent proximal end. **(B)** After the artery was straightened by the first micro-guidewire with the stent proximal end being opened, the second micro-guidewire (double short arrows) was sent right through the opened proximal end for deployment of a supporting stent.

DISCUSSION

Atherosclerosis frequently involves the intracranial vertebral artery on bilateral sides (13, 14). Patients with atherosclerotic occlusion of both intracranial vertebral arteries often experience recurrent attacks of visual disturbance, dizziness, ataxia, or disability (14). Collateral circulation may provide baseline perfusion for some patients but fail to supply sufficient blood at times of increased oxygen demand, leading to lifestyle-limiting symptoms. The optimal treatment approaches for patients with intracranial vertebral artery occlusion is rarely analyzed. Given the high incidence and recurrent symptoms in spite of antiplatelet treatment, revascularization of the occluded intracranial vertebral artery using endovascular stenting and angioplasty has been attempted within the past decade and considered to be technically accessible because of fast development of endovascular management. However, the safety and efficacy of endovascular stenting and angioplasty still need further investigation (15–17). During the recanalization of intracranial vertebral artery occlusion, the major technical challenge is traversing the occlusion site with a guidewire even though other factors, such as the length and stage of the occlusion, may also affect the feasibility and outcome.

In this case report, occlusion of the right vertebral artery at the V4 segment was treated with endovascular stent angioplasty. During the intervention, the proximal end of the Enterprise stent was collapsed in the curved vertebral artery after withdrawal of the stent delivery system, resulting in reduced blood flow through the stented artery. The collapsed stent end was successfully rescued by deploying a balloon-expandable Apollo stent using the technique of double micro-guidewires. The deployment of the first micro-guidewire straightened the vertebral artery and reopened the stent proximal end, which facilitated passage of the second micro-guidewire through the opened proximal stent end into the stent lumen for deployment of the Apollo stent to support the proximal end of the Enterprise stent. When navigating the second micro-guidewire into the stent proximal end, try not to rotate the micro-guidewire too much. This technique of double micro-guidewire rescue is also useful for collapsed stents in other curved arteries, especially those with atherosclerotic stenoses that may compress the stent end after withdrawal of the stent delivery system, resulting in collapse of the stent proximal end and decreased blood flow.

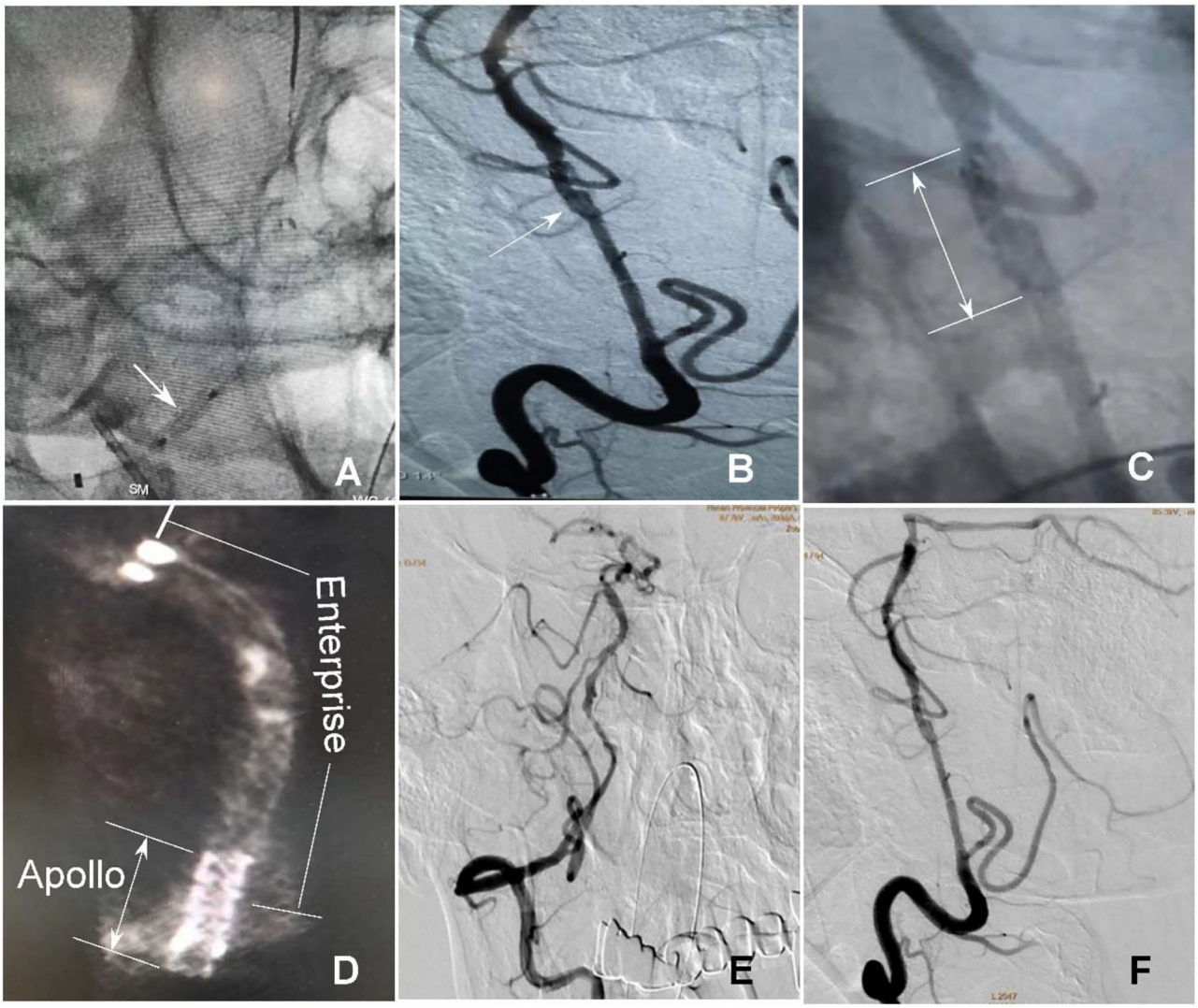

FIGURE 4 | Rescue management of the collapsed stent end. **(A)** An Apollo stent (2.5 × 10 mm) was navigated along the 200-cm micro-guidewire to the proximal end of the Enterprise stent and expanded for deployment (arrow). **(B)** The Apollo stent was deployed to partially overlap with the Enterprise stent (arrow). **(C)** The arrow indicates the deployed Apollo stent. **(D)** DynaCT scan demonstrated partial overlap of the distal Enterprise stent with the proximal Apollo stent. **(E,F)** After stenting, both stents were well-patent with favorable forward flow.

An arterial curvature may cause the stent proximal segment to form an angle with the curved artery, thus leading to collapse or incomplete opening of the stent proximal end, reduced blood flow, or even complete occlusion of the arterial segment. Elastic retraction of the stenotic vessel may also cause collapse of the stent proximal end if insufficient balloon predilation is performed at the stenotic vascular segment. Insufficient length of the stent may also cause the stent proximal end to collapse because the stent is not long enough to cover the whole stenosis. Rich experience of endovascular maneuver, gentle handling of endovascular devices, sufficient length of the stent deployed, and sufficient balloon predilation of the stenotic vascular segment help reduce intraprocedural complications, especially when withdrawing the stent delivery system. Rude operation may cause an angle formed between the stent and the artery wall, leading to stent collapse and reduced blood flow. Short segments of occlusion are easy to reopen, whereas a long segment of occlusion of a curved artery may readily cause stent deformation and even occlusion, which needs immediate rescuing measures to prevent possible ischemic events.

In endovascular treatment of cerebrovascular diseases, the double micro-guidewire technique is used to increase catheter stability (18), facilitate stent navigation through tortuous arteries (19, 20), and help "Y" configuration stenting in middle cerebral artery bifurcation aneurysms (21) or coil embolization of aneurysms located in the posterior circulation (22). The role of a second micro-guidewire

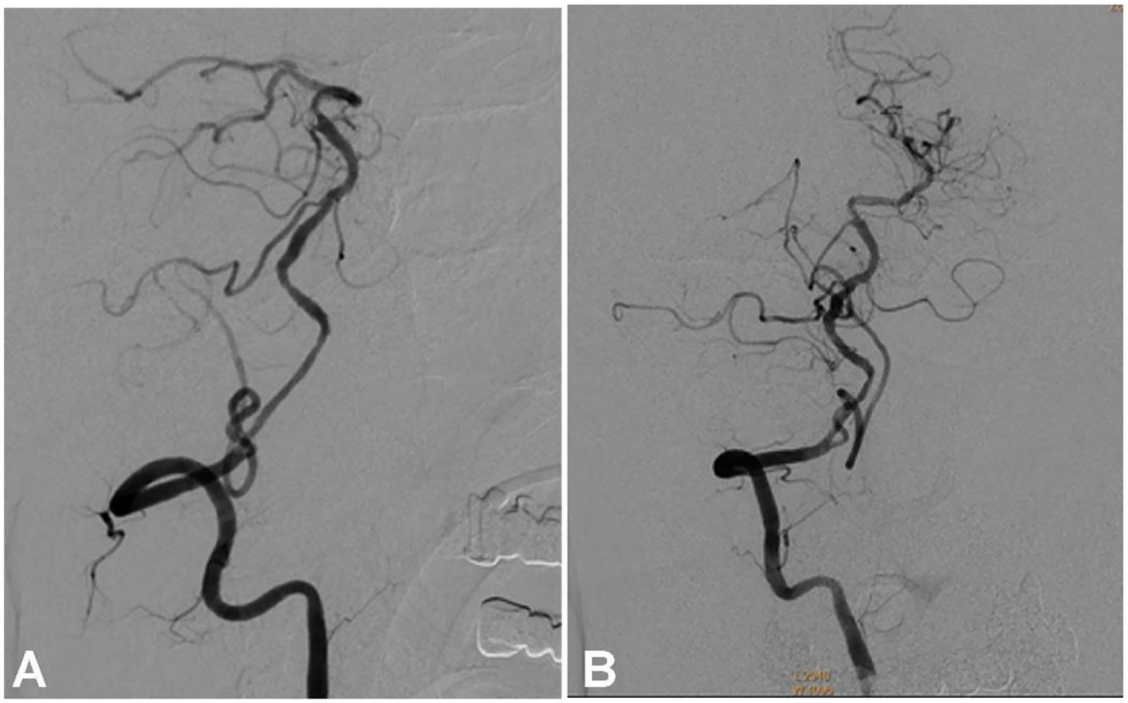

FIGURE 5 | Follow-up angiography at 6 months after stenting demonstrates unobstructed blood flow through the stented vertebral artery **(A,B)** with no stenosis.

is certainly associated with straightening of the tortuous cerebral artery to facilitate subsequent endovascular maneuver. In our case, the double micro-guidewire technique was used to rescue the collapsed stent proximal end because stent collapse may lead to serious complications of stent occlusion, thrombosis, and ischemic events. The first micro-guidewire passed through the proximal lateral stent mesh into the stent lumen, which not only straightened the tortuous vertebral artery, but also reopened the collapsed stent proximal end. It was, thus, helpful for navigation of the second micro-guidewire right through the opened stent proximal end into the stent lumen for deployment of a supporting stent to prevent collapse of the stent proximal end. When faced with a collapsed stent end in tortuous cerebral arteries, immediate action is needed to rescue the seemingly imminent severe complications of ischemic events. This case report presented an effective approach for solving this severe issue.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Henan Provincial People's Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KZ and Z-LW: study design. KZ, J-CX, H-LG, B-LG, and Y-FW: data collection. KZ, J-CX, H-LG, and B-LG: data analysis. T-XL: supervision. KZ: writing of the original version. B-LG: revision. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Case Report: Anterior Spinal Cord Ischemia Following Embolization of Cerebellar Arteriovenous Malformation: An Illustrative Case and Review of Spinal Cord Vascular Anatomy

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Spinal cord ischemia (SCI) is a rare entity with high mortality and morbidity which can arise from causes such as atherosclerosis, aortic dissection or aneurysm, thromboembolic events or systemic hypotension, and is a potential complication of spinal surgery. Published literature contains very few reports of SCI as a complication of intracranial interventions, highlighting the uncommon nature of SCI in these circumstances. We report the occurrence of anterior SCI in a 69-year-old patient following successful embolization of a cerebellar arteriovenous malformation (AVM), marked by upper extremity weakness, lower extremity paraplegia, loss of bladder and bowel control, and hypercapnic respiratory failure requiring mechanical ventilation. Magnetic resonance imaging (MRI) demonstrated upper cervical diffusion restriction and T2/STIR hyperintensity. Unusually, SCI occurred in this case without intraprocedural catheter wedging or obvious flow limitation, prolonged procedure time, hypercoagulable state, or general hypotension. We review previous cases in the literature as well as spinal cord vascular anatomy, and discuss the possible etiologies of this complication. Spinal cord ischemia could be a very rare complication of neuroendovascular procedures even in the absence of warning signs and should be carefully evaluated in patients with suspected neurologic symptoms after such procedures.

Keywords: stroke, spinal cord ischemia, arteriovenous malformation, embolization, vascular diseases, spinal cord

INTRODUCTION

Spinal cord ischemia (SCI), a rare entity with high mortality and morbidity, can be related to various etiologies including atherosclerosis, aortic dissection/aneurysm, cardiac emboli, and systemic hypotension. It mostly involves the anterior spinal cord (1–3). The incidence of SCI as a complication of intracranial interventions is very rare and has only been described in three case reports (3–5). Herein, we report the fourth known case of such

complication following a neurointerventional procedure, an anterior SCI subsequent to embolization of a cerebellar arteriovenous malformation (AVM), and discuss the possible etiologies of this complication to highlight the importance of careful assessment of patients with suspected neurologic symptoms for SCI after neuroendovascular procedures.

CASE DESCRIPTION

The patient was a 69-year-old female with a past medical history of atrial fibrillation, hypertension, hyperlipidemia, and hypothyroidism. She denied any family history of neurovascular disease, AVM, or aneurysm. A right cerebellar hemispheric AVM was discovered incidentally during workup for dizziness. She had undergone neurologic work-up for intermittent vertigo 2 years before the admission, which in turn had resulted in the discovery, on brain MRI, of a right cerebellar hemispheric lesion, thought to represent a cavernous malformation (CM). At that time, she did not have any complaints of headache, motor or sensory disturbances, or loss of bladder or bowel control. Her neurologic evaluation was intact. Thus, she was being followed up by brain MRI and neurologic examination annually. The repeat MRI brain during her second year of follow up was interpreted as demonstrating an AVM rather than a CM, and she was scheduled for cerebral angiography to confirm the diagnosis.

Angiography revealed a 2.5 cm pial AVM in the superomedial right cerebellar hemisphere, abutting the tentorium. The AVM was supplied primarily through branches of a hypertrophied right superior cerebellar artery (SCA), with lesser arterial supply provided by distal branches of the right posterior inferior cerebellar artery (PICA) (**Figure 1**). A single short superficial cerebellar vein drained the AVM into a right cerebellar tentorial vein, and then into the right transverse sinus. Two small nidal aneurysms were also identified, the largest of which measured 1.8 mm in maximal dimension. Magnetic Resonance T2 gradient echo imaging demonstrated small foci of susceptibility in the region of the AVM, presumably reflecting small areas of chronic hemosiderin deposition, but there was no evidence of recent hemorrhage. The vertebral arteries were relatively co-dominant.

After neurosurgical consultation, surgical resection of the AVM was recommended, and pre-surgical embolization was requested to minimize the risk of intraoperative bleeding.

Embolization was performed under general anesthesia. Blood pressure, heart rate, and oxygen saturation were monitored intra-procedurally. The mean arterial pressure (MAP) averaged 94.5 mmHg (range 76–117 mmHg) and no hypoxia or hypotension occurred throughout the procedure. Using ultrasound guidance, a five French shuttle guide sheath was placed into the right common femoral artery. Heparin was administered intravenously with intermittent bolus administration to maintain therapeutic anticoagulation. Activated Clotting Time was monitored, with an average value of 201 and a baseline of 135.

The sheath was advanced over a four French angled vertebral catheter into the proximal cervical left vertebral artery (VA). As noted on the diagnostic angiogram, the left VA had a variant origin, arising directly from the aortic arch, and was chosen for access due to marked tortuosity at the origin of the right VA. Five micrograms of intra-arterial verapamil was administered to prevent vasospasm, and the five French guide sheath was advanced to the mid-cervical left VA, beyond the origin of the artery of cervical enlargement, which was visualized on roadmap digital subtraction angiograms (DSA). The vertebral catheter was removed and DSA was performed through the sheath. There was good flow around the five French sheath without evidence of any contrast stagnation to suggest flow compromise or occlusion of the VA (**Figure 2**). The AVM was unchanged compared to the angiogram 2 months earlier.

Next, a Phenom Plus delivery catheter and Apollo microcatheter were advanced coaxially over a microwire through the five French sheath, with the Phenom Plus catheter terminating in the distal cervical left VA. An Apollo microcatheter was first taken distally into the dominant SCA branch supplying the AVM, and Onyx 34 was used to embolize a portion of the AVM nidus. The Apollo microcatheter was slowly removed, and the tip detached, remaining in the right SCA. Next, a new Apollo microcatheter was taken into a second SCA branch supplying the AVM, and additional Onyx was administered. This microcatheter was removed, without tip detachment. Finally, an SL-10 microcatheter was advanced into an inferior branch of the right SCA supplying the AVM, and a small amount of Onyx was administered before removing the microcatheter.

The remaining branches of the right SCA supplying the AVM were not easily catheterized. Embolization had resulted in an approximately 50% reduction in the size of the AVM nidus, so a decision was made to terminate the exam. Post-embolization intracranial and cervical angiography demonstrated patency of the arteries of the posterior circulation and the extracranial and intracranial segments of the left VA. The artery of cervical enlargement and the ASA remained patent at completion of the procedure. The sheath was removed, and hemostasis achieved. A Cone beam CT demonstrated expected post-procedural changes.

The patient was extubated and transferred to the intensive care unit. She was slow to awaken from general anesthesia, but was oriented, following commands, and moving all extremities antigravity immediately post-extubation.

On evaluation 3 h post-procedure, she was sleepy but easily aroused by voice, and could follow simple commands. Her neurologic examination at that time was intact. Additionally, she had bilateral upper extremity strength of at least 4/5 and intact light touch sensation throughout. Over the next 2 h, her condition mostly remained unchanged, with mild weakness of bilateral upper extremities on examination that was suspected to be limited by the element of effort and of position, given otherwise normal findings. She was reported to have general weakness at approximately 8 h after the procedure. Her situation did not improve after 2 h and required a repeat of examination and further evaluation.

Abbreviations: AP, anteroposterior; ASA, anterior spinal artery; AVM, arteriovenous malformation; DSA, digital subtraction angiograms; MAP, mean arterial pressure; MRI, magnetic resonance imaging; PICA, posterior inferior cerebellar artery; SCI, spinal cord ischemia; SCA, superior cerebellar artery; VA, vertebral artery.

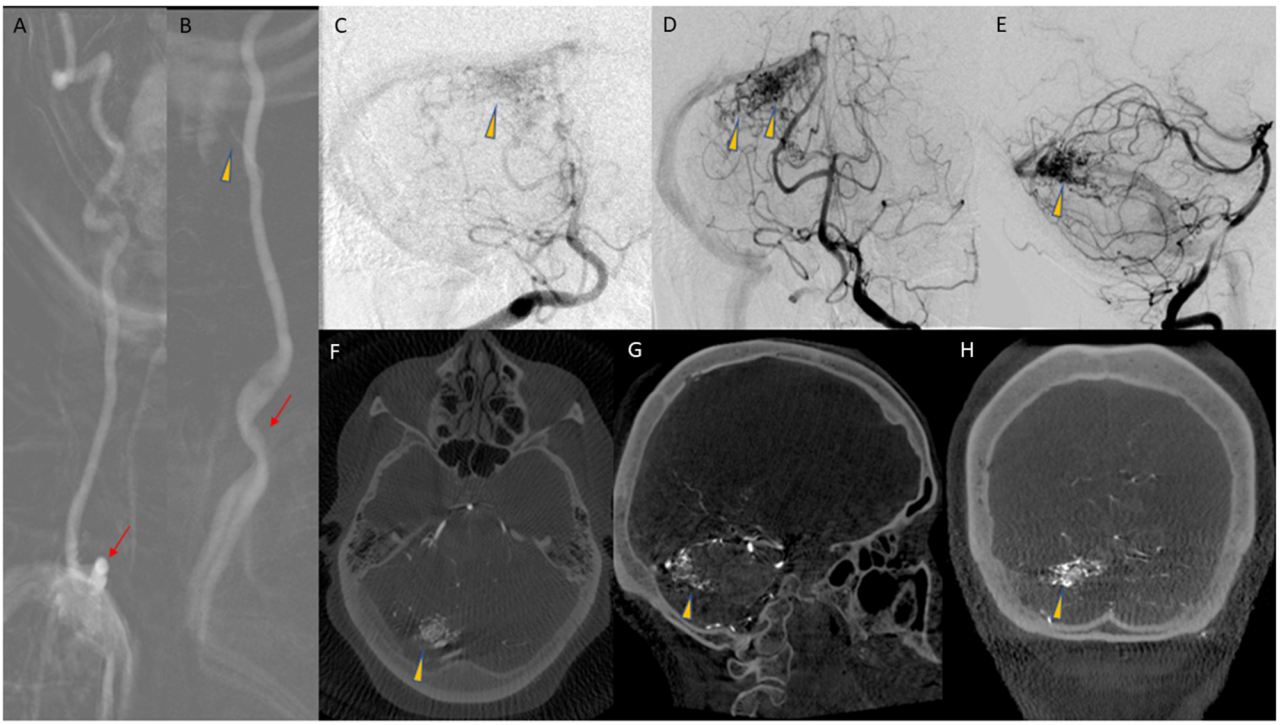

FIGURE 1 | (A) AP roadmap image of co-dominant right VA, with tortuous origin (arrow) from the subclavian artery. **(B)** AP roadmap of left VA origin (arrow) and proximal cervical course of the artery. The artery of cervical enlargement is also seen (arrowhead). **(C)** AP angiogram from a right VA injection, with opacification of the AVM nidus (arrowhead), with competitive flow from the left VA. **(D,E)** AP and lateral arterial phase images from a left VA injection, demonstrating the AVM nidus (arrowheads) in the superior aspect of the right cerebellar hemisphere. **(F–H)** Reconstruction of 3D DSA data in axial **(F)**, Sagittal **(G)**, and coronal **(H)** planes, demonstrating the AVM nidus (arrowheads).

Her examination, approximately 10 h post-embolization, revealed strength of 3–4/5 in both upper extremities. Her lower extremities strength remained 5/5, with normal pinprick and vibration sensory exam throughout. Her vital signs were within normal limits and stable, and her examination was otherwise unremarkable. However, concern for ischemia prompted a Magnetic Resonance Imaging (MRI) brain, which suggested diffusion restriction in the upper cervical spinal cord, although this was sub-optimally evaluated due to motion artifact. A cervical spine MRI was obtained next and demonstrated T2/STIR hyperintense signal at the C1 level, corresponding to the region of restricted diffusion reported on MRI of the brain, raising suspicion for possible cord infarction. The patient's upper extremity weakness continued to progress over the subsequent 8 h despite maintaining MAP >75 mmHg, and stable vital signs, and she developed new intermittent lower extremity weakness, but light touch sensation remained intact in all extremities. Clinical examination at this point was consistent with acute SCI. A second cervical MRI revealed more extensive abnormal signal centered at the C2 and C3 levels with associated cord expansion. Additionally, new signal abnormality had developed at the C5–C6 level, without associated cord expansion (**Figure 3**). Her limb weakness continued to progress. On evaluation 1 day post-procedure, she had a strength of 1/5 and 2/5 in proximal and distal muscle groups of both upper extremities, respectively, with a strength of 2/5 in both lower extremities. Pinprick and temperature sensation were decreased at the approximate level of C2–C4 throughout the lateral torso and both upper extremities, while vibration and proprioception remained intact in all extremities. These findings reinforced the diagnosis of acute SCI. **Figure 4** demonstrates the timeline of the events within 24 h after the procedure. A second brain MRIat this time showed evidence of T2/FLAIR hyperintense signal and increased diffusion restriction in the right cerebellar hemisphere at the site of Onyx embolization. As a result of the SCI, she developed hypercapnic respiratory failure requiring urgent endotracheal intubation and mechanical ventilation. She eventually required tracheostomy placement for anticipated prolonged ventilator weaning along with percutaneous gastrostomy placement. She was successfully weaned off the ventilator and resumed oral intake by 3 weeks, and underwent acute inpatient rehabilitation for a total 4 months, and is now residing at home with significant assistance.

DISCUSSION

Arterial supply to the spinal cord can be divided into (1) the intrinsic arteries, located within the cord's substance, (2) the extrinsic arteries of the spinal canal, which travel

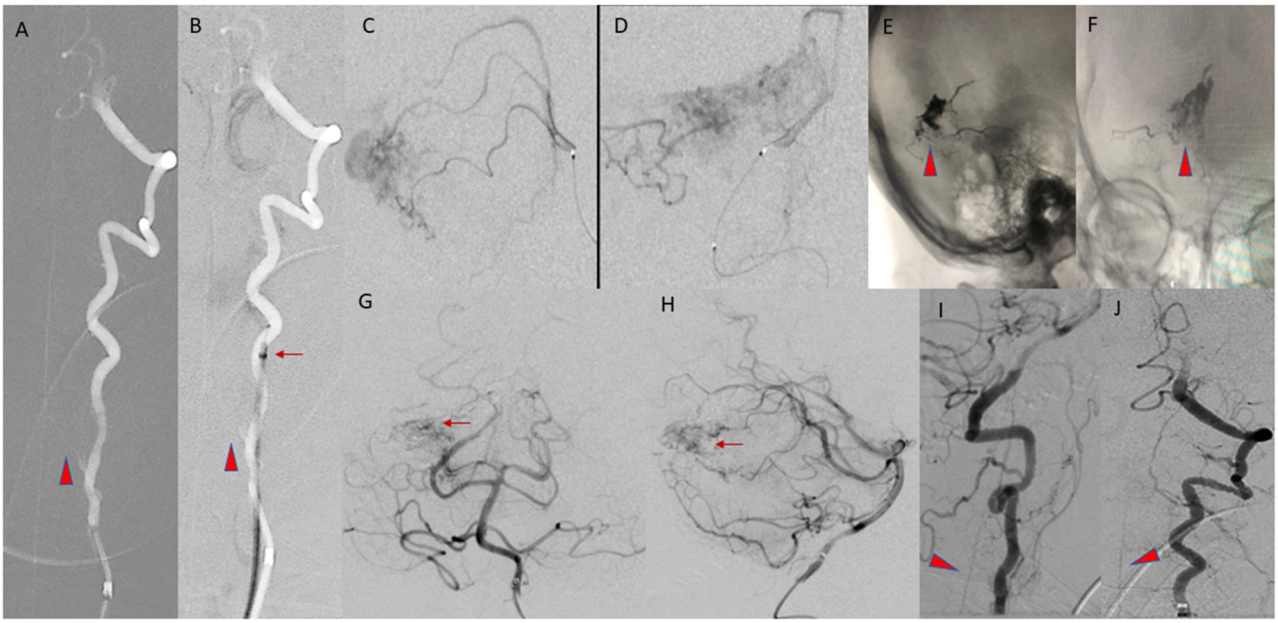

FIGURE 2 | (A,B) AP Roadmap images of the left VA, before **(A)** and after **(B)** advancement of the five Fr guide sheath into the mid cervical left VA, distal to the origin of the artery of cervical enlargement (arrowheads). The position of the tip of the guide sheath is marked by the arrow. **(C,D)** Lateral and AP views of a right superior cerebellar artery microcatheter injection, during embolization of the AVM. **(E,F)** Final cast of the Onyx (arrowheads) within the AVM nidus. **(G,H)** Final AP and lateral arterial phase images of the posterior circulation, from a left VA injection, demonstrating the residual nidus (arrows). **(I,J)** Lateral and AP images from the final left VA injection prior to removal of the guide sheath, demonstrating patency of the ASA (arrowheads).

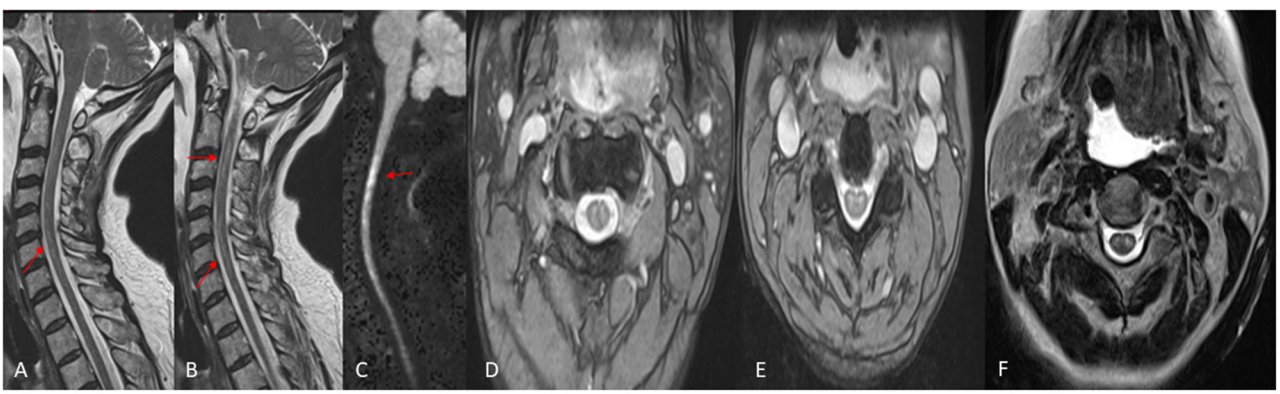

FIGURE 3 | MRI Cervical Spine, performed the day following the embolization. **(A,B)** Sagittal T2W images demonstrating abnormal increased T2 signal in the spinal cord (arrows). **(C)** Sagittal Diffusion Weighted image demonstrating abnormal diffusion restriction in the Cervical Spinal cord (arrows). **(D,E)** Axial GRE T2W images demonstrating abnormal increased signal in the central Gray matter, or "owls eye" sign. **(F)** Axial TSE T2W image demonstrating the "owls eye" sign.

longitudinally and circumferentially along the cord's surface, and (3) the radiculomedullary and radiculopial arteries, which enter the spinal canal from the extraspinal vasculature at variable segmental levels.

The intrinsic arteries of the spinal cord can be anatomically separated into central and peripheral systems. The central system is supplied by the sulco-commissural arteries, which arise from the anterior spinal artery (ASA) and supply the majority of the central gray matter. In this system, blood flows from the center of the spinal cord to the periphery. The peripheral intrinsic system is supplied by radial perforating arteries that originate from the pial network, a highly variable network of arteries that branch from both the ASA and posterior spinal artery (PSA) to encircle the spinal cord. The peripheral system primarily perfuses the white matter of the spinal cord, and through the PSAs supplies the dorsal columns of the gray matter.

The ASA, paired PSAs, and the circumferential pial network comprise the extrinsic arterial system of the spinal canal.

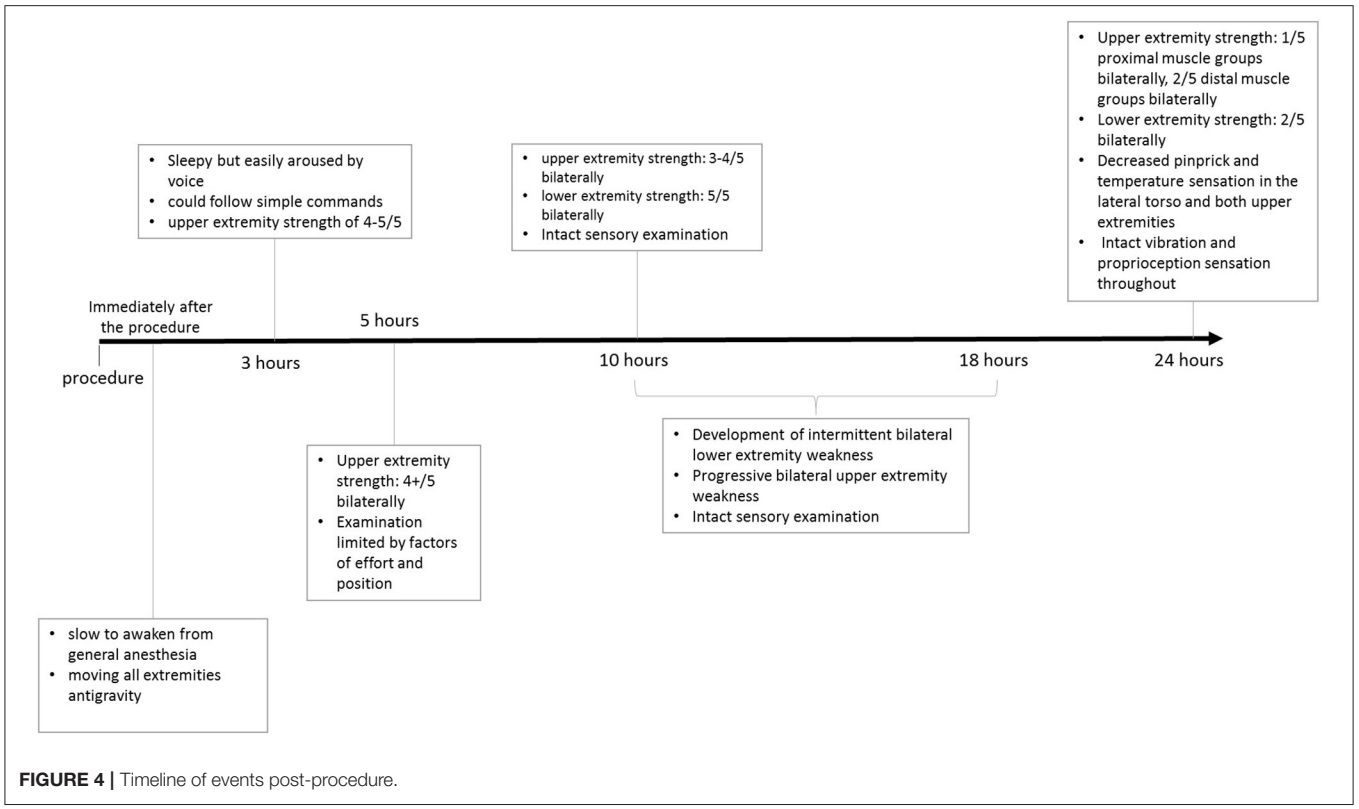

FIGURE 4 | Timeline of events post-procedure.

The ASA, the dominant artery of the spinal vasculature that supplies the anterior two-thirds of the cord, is derived from branches arising from the intracranial segments of both VAs, and travels inferiorly along the ventral surface of the spinal cord, although in some cases, the ASA can arise from the intracranial segment of a single VA. The ASA is further supplied by anastomoses to a variable number of radiculomedullary arteries (**Figure 5**) throughout the cervical, thoracic, and lumbar spine, which range from 6 to 10 in number (6). The paired PSAs originate either from the intracranial VAs proximal to the PICAs or from the proximal PICAs. These arteries travel longitudinally and discontinuously along the dorsolateral surface of the cord, with variable contributions from radiculopial segmental branches.

Radiculomedullary and radiculopial arteries supply the ASA and the PSAs, respectively (1, 7, 8). The largest cervical radiculomedullary artery is often called the artery of cervical enlargement (7, 9). The number of sizable radiculomedullary and radiculopial arteries supplying the cervical cord varies. Haller reported as many as 11 radiculomedullary arteries and one radiculopial artery in the cervical spine (10), while Adamkiewicz observed three sizable radiculomedullary branches and one or two radiculopial arteries (11). Subsequent cadaveric studies reported a variable range of radiculomedullary arteries between 1 and 6 (10). Chakravorty found that most commonly, two or three radiculomedullary arteries $>250\,\mu m$ in size contribute to the ASA in the cervical spine, typically arising from C4, C5, or C6 radicular arteries. He also reported that the number of major radiculomedullary vessels in the cervical spine measuring $>500\,\mu m$ was never more than two, and only a single major radiculomedullary branch of this size was present in 12 of 31 spinal cords studied (10). The pial network, ASA, and PSAs create a rich vascular supply to the cervical spine, decreasing the likelihood of ischemia in most patients. However, due to the high degree of anatomic variability, in some individuals a paucity of radiculomedullary arteries can increase the risk of anterior SCI when provoked by local or systemic hemodynamic insufficiency (4).

Spinal cord ischemia has various manifestations including paraplegia, sensory deficits and urinary incontinence (12). Anterior SCI can present with bilateral motor dysfunction and pain and temperature sensation disturbance below the level of infarction with preserved posterior column pathways, supporting vibration and proprioception (13). Spinal cord ischemia has been reported following numerous surgeries including spinal surgeries as well as aortic and cardiac interventions (2, 4, 14, 15), but onset after an intracranial intervention is very rare, reported only by a few publications (3–5). In all prior reports, including our own, infarction occurred in the cervical region.

A case of unilateral posterior cervical SCI following vertebral angioplasty was attributed to flow reversal in the VA due to a persistent stenosis in the VA, resulting in hypoperfusion or thromboembolism in the ipsilateral PSA (3).

In three cases of cervical SCI following embolization of basilar tip aneurysms involving the use of six French or seven French guide catheters, the authors posited that wedging of the catheter in the VA may have resulted in thromboembolic occlusion or flow restriction of radiculomedullary branches of the VA supplying

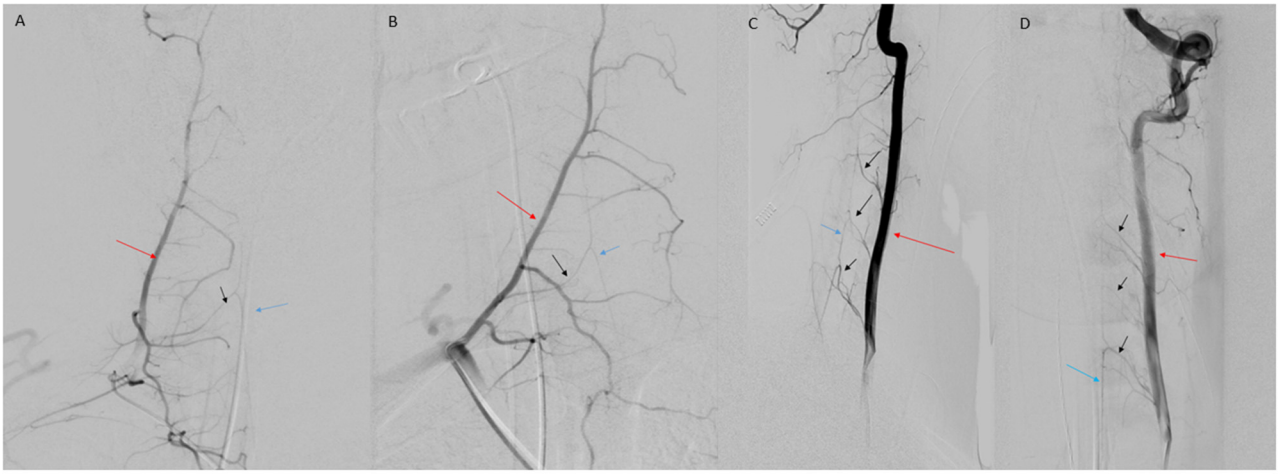

FIGURE 5 | (A) AP view of right deep cervical artery (red arrow) injection demonstrating radiculomedullary feeder (black arrow) to the ASA (blue arrow). **(B)** Oblique view of deep cervical artery (red arrow) injection demonstrating radiculomedullary artery (black arrow) supply to the ASA (blue arrow). **(C)** Lateral view of VA (red arrow) injection demonstrating multiple cervical radiculomedullary feeders (black arrows) to the ASA (blue arrow). **(D)** AP view of left VA (red arrow) injection demonstrating multiple cervical radiculomedullary feeders (black arrows) to the ASA (blue arrow).

the cervical spinal cord. They proposed downsizing the guide catheter to five French as a possible solution. We utilized a five French guide sheath (similar outer diameter to a seven French guide catheter), without angiographic evidence of "wedging" or flow arrest during the procedure.

Hypotension resulting in infarction at watershed areas of the cervical spinal cord located in between radiculomedullary arterial anastomoses is unlikely in this case, as the MAP was stable throughout the embolization with no evidence of hypotension. Thromboembolic events in the VA, ASA, or the artery of cervical enlargement are unlikely as these arteries were patent in the post-embolization left VA angiogram, and additionally, the tip of the five Fr sheath was beyond the origin of the artery of cervical enlargement.

This is an unusual case of successful embolization of a cerebellar AVM through the posterior circulation complicated by cervical SCI, without catheter wedging/flow arrest, prolonged procedure time, hypercoagulable state, or general hypotension. It is likely that with the use of a five French sheath in the left VA, which is comparable in diameter to a six or seven French guide catheter, and even in the absence of catheter wedging and flow limitation, there was enough reduction in perfusion pressure to the ASA through the artery of cervical enlargement to cause SCI. We speculate that this patient and the other reported similar cases may have occurred in patients who happened to have a reduced number of radiculomedullary suppliers to the ASA. Spinal cord ischemia can be a very rare complication of neuroendovascular procedures even in the absence of warning signs and should be carefully evaluated in patients with suspected neurologic symptoms after such procedures.

Given the rarity of SCI relative to the large numbers of endovascular procedures where the VA is accessed with guide sheaths and catheters, it remains unclear whether one can recommend a thorough assessment of spinal cord arterial supply prior to every endovascular intervention in the posterior circulation. Most anatomic series and textbooks indicate an average of 2–3 radiculomedullary arteries supplying the ASA at the level of cervical spinal cord. However, the high degree of variation in the number of radicullomedullary arteries, puts patients with paucity of radicullomedullary arteries at a greater risk for developing spinal ischemic events following intracranial endovascular interventions in the posterior circulation. Although rare, given the high morbidity and mortality of such complication, it seems reasonable to recommend a thorough assessment of spinal cord arterial supply before endovascular interventions, for patients in whom the artery of cervical enlargement originates from the VA that is planned to be accessed via a guide sheath or catheter. Also, consistent with prior reports we suggest downsizing from a 5 F guide sheath might be a solution to reduce the risk of this rare and devastating complication in such patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

This study was granted a waiver of consent by the Northwestern University Institutional Review Board (STU00213955).

AUTHOR CONTRIBUTIONS

YM, DRC, and RNA collected the patient's material. RNA, AB, and AS were responsible for clinical examination of the patient. RNA, MCH, SAA, EJR, and AS reviewed patient's imaging. YM,

DRC, JRC, and AS wrote the manuscript. DRC, JRC, AB, MCH, SAA, and EJR edited the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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First off Label Endovascular Clinical Experience to Treat Diffuse Cerebral Venous Sinus Thrombosis Using the INARI FlowTriever System: Case Report

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Anticoagulation with heparin is the current mainstay treatment for Cerebral Venous Sinus Thrombosis (CVST). Endovascular treatment is increasingly being used to treat patients with CVST who are non-responsive to anticoagulation. These more aggressive interventions include catheter-based local chemical thrombolysis, balloon angioplasty and mechanical thrombectomy with uncertain safety and efficacy. Here we describe the first reported clinical experience using the INARI FlowTriever system to treat a patient presented with focal weakness and found to have diffuse CVST.

Keywords: cerebral venous sinus thrombosis, INARI FlowTriever system, endovascular treatment, intervention, case report

INTRODUCTION

Cerebral Venous Sinus Thrombosis (CVST) is a rare stroke with a wide range of symptomatology at presentation ranging from headache, focal weakness, and coma. Anticoagulation remains the mainstay of treatment. However, in a subset of patients; endovascular treatment can be potentially beneficial. Here we describe the first reported clinical experience using the INARI FlowTriever system to treat a patient presented with focal weakness and found to have diffuse CVST.

CASE REPORT

A 78-year-old female with past medical history including autoimmune hepatitis, hypothyroidism. She presented to the hospital via emergency medical services with left arm weakness and jerky movements. This event was witnessed by family while she was eating. No recent trauma or fall. No earache, hearing loss, or discharge. No loss of consciousness reported. Of note, she is on azathioprine for autoimmune hepatitis. She was evaluated by the stroke team upon arrival. Vital signs included: elevated blood pressure at 153/72 mmHg, normal pulse 91, and normal respiratory rate at 17. She was afebrile. Laboratory work up revealed normal white cell count (WBC) of 7.2 10^9/L, and normal hemoglobin of 12 gm/dL. Platelets noted to be low at 80 10^9/L. Serum chemistry was unremarkable except for low sodium of 129 mEq/L. Urine toxicology drug screen was negative. COVID-19 PCR (polymerase chain reaction) test was negative.

A Computed Tomography (CT) head on admission revealed left temporoparietal intraparenchymal hemorrhage, right frontal sulcal subarachnoid hemorrhage, and left parietal sulcal subarachnoid hemorrhage. Vessel images with Computed Tomography Angiogram (CTA) head and neck revealed extensive venous sinus thrombosis involving superior sagittal sinus, bilateral transverse, and sigmoid sinuses. She subsequently underwent Magnetic Resonance Imaging (MRI) of the brain with and without contrast and Magnetic Resonance Venogram (MRV) which confirmed extensive venous sinus thrombosis and multicompartment bleeding. No restricted diffusion noted (**Figure 1**).

Patient was evaluated by interventional neurology, neurosurgery, and neuro critical care team. She was started on levetiracetam for symptomatic treatment of focal seizures with left upper extremity shaking. She was started on anticoagulation with heparin drip and was admitted to neuro ICU for close neurological monitoring.

Desired therapeutic level of activated Partial Thromboplastin Time (aPTT) at 67.2 s was achieved at 24 h and patient remained in the neuro critical intensive care unit. After a thorough multidisciplinary team discussion due to persistent left-sided weakness, diffuse CVST, multicompartment bleeding while being on anticoagulation, low platelets, and anticipation of moderate to high risk of unfavorable outcome; the decision was to perform endovascular mechanical venous thrombectomy (Approximately 48 h after admission). She underwent a successful mechanical venous thrombectomy using the INARI FlowTriever system with large clot burden extracted. She remained clinically stable after the procedure and her left upper extremity weakness improved at day 5. No new symptomatic ICH. The 22 French (7.33 mm) venous access was sutured with figure of 8 technique followed by manual pressure. No post-procedure groin complications noted. She was switched to novel oral anticoagulation prior to discharge. During the 3 months follow-up–MRI brain with and without contrast revealed near complete resolution of the clot burden in superior sagittal sinus and left transverse-sigmoid complex. Her 3 months modified Rankin score was at 0. She was resumed on apixaban for 12 months with a follow-up brain magnetic resonance venogram planned.

MECHANICAL ENDOVASCULAR VENOUS THROMBECTOMY: PROCEDURE DETAILS

The patient was brought to the interventional suite by the anesthesia team and placed in a supine position on the angiogram table. Patient arrived intubated. The right radial region was prepped, draped and cleaned in a sterile fashion. The right radial artery was accessed with ultrasound guidance using a micropuncture needle and a 5 French by 10 cm introducer sheath was placed. Radial cocktail was given to minimize vasospasm. Subsequently, a 5 French glide catheter was advanced over a Glidewire to select the right internal carotid artery under fluoroscopy guidance. Right internal carotid angiogram run revealed filling defects in the mid to posterior aspect of superior sagittal sinus, right transverse, and right sigmoid sinus consistent with diffuse venous sinus thrombosis. There is venous congestion and no venous outflow noted in the left transverse and sigmoid sinuses.

The right common femoral vein was accessed with ultrasound guidance using a single wall needle technique and a 5 French short sheath was placed. Subsequently an 8 French, 10 French, 14 French and then 18 French dilators were sequentially used before introducing a 22 French venous sheath (GORE DrySeal Flex Introducer Sheath). The sheath was connected to a syringe and inflated to stop venous blood backflow. Then a 5 French select catheter was advanced over a Glidewire to the right atrium, superior vena cava, then to select the left internal jugular vein. The Glidewire was subsequently removed and TAD2 tapered peripheral wire (0.035–0.018 260 cm) was advanced through the select catheter and parked in the distal left internal jugular vein at close proximity to the jugular bulb level. Then the INARI Triver20 was advanced over the TAD2 (Over-the-wire technique) to the left jugular bulb. Of note, there was no difficulty noted to advance the large bore aspiration catheter (INARI Triver20) into the internal jugular vein over the stiff TAD2 wire. Then under fluoroscopic guidance the Rebar 021 microcatheter was advanced over Victory 18 microguidewire into the superior sagittal sinus crossing the thrombus. Then solitaire stent retriever 6 x 40 mm was advanced through the Rebar microcatheter and was successfully deployed across the mid aspect of the superior sagittal sinus. The Rebar microcatheter was then removed. Multiple attempts to advance the FlowTriver Catheter over the solitaire wire through the INARI Triver20 into the left transverse sigmoid complex was unsuccessful. Amplatz Super Stiff wire 0.035 $\times$ 260 cm was then used to advance the INARI Triver20 aspiration catheter further distally. However, it was challenging to cross the jugular foramen with either the INARI Triver20 or the FlowTriver Catheter. Subsequently the FlowTriver Catheter was removed and Vect074 reperfusion catheter was advanced over the Solitaire stent retriever wire through the Triver20 large bore aspiration catheter, then the Vect074 was advanced to the proximal aspect of the Solitaire stent retriever in the mid posterior sagittal sinus (was advanced back and forth over the Solitaire stent retriever wire under continuous aspiration with negative pressure connected to the penumbra pump through the Vect074). Then the Vect074 reperfusion catheter and Solitaire stent retriever was removed from the body as one piece through the Triver20 large bore aspiration catheter with negative pressure applied using a 60 cc syringe. Multiple large red clots noted in the the FlowTriver Catheter aspirate. Total fluoroscopy time is 50.8 min, and 70 cc Visipaque 270 low osmolar contrast was used (**Figure 2**: Procedure technique).

DISCUSSION

Here we discussed a patient with diffuse cerebral venous sinus thrombosis who was treated initially with large molecular weight heparin drip with a desired therapeutic aPTT level. The patient was deemed moderate to high risk of unfavorable outcome and was subsequently underwent mechanical endovascular venous

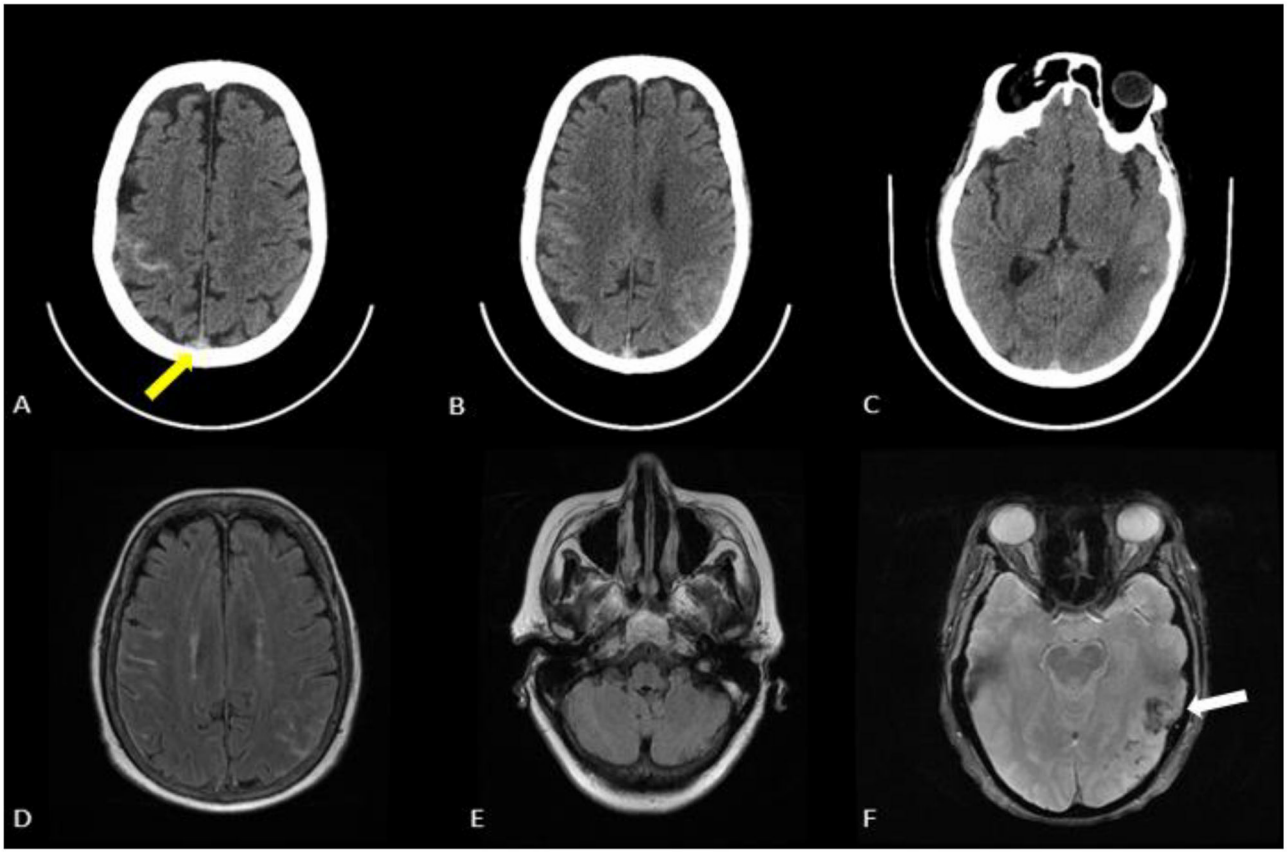

FIGURE 1 | (A–C) CT head revealing acute multicompartment hemorrhages with left temporal parietal intraparenchymal hemorrhage measuring approximately 3 cm, right frontal subarachnoid hemorrhage and left parietal subarachnoid hemorrhage. No midline shift noted. Hyperdense sign noted (yellow arrow) in the superior sagittal sinus suggesting venous sinus thrombosis. **(D,E)** MRI brain without contrast FLAIR sequence with right frontal hyperintensity and left parietal hyperintensity consistent with subarachnoid hemorrhage. **(F)** Left temporal blooming noted (white arrow) on the GRE sequence consisted with intraparenchymal hemorrhage.

thrombectomy using the INARI FlowTriever system and large clot burden was aspirated with a reasonable safety profile.

The FLARE (FlowTriever Pulmonary Embolectomy Clinical Study) is a prospective single-arm, multicenter investigational device trial in patients with acute intermediate risk pulmonary embolism using the INARI FlowTriever system (Inari Medical, Irvine, California) (1). This study revealed an acceptable effectiveness profile compared to catheter directed thrombolysis with an average right ventricle/left ventricular risk reduction of 0.38 (25% risk reduction), and a favorable safety profile with major adverse events rate at 3.8%. Major adverse events included any of the following within 48 h of treatment: device-related death, major bleeding, treatment-related clinical deterioration, treatment-related pulmonary vascular injury, and treatment-related cardiac injury.

Endovascular treatment for CVST remains a challenge in the neuro interventional field. Anticoagulation is the mainstay first line treatment for Cerebral Venous Sinus Thrombosis (CVS T) according to American stroke Association/American Heart Association and European guidelines (2, 3). However, a small subset of patients would potentially benefit from endovascular treatment but it still uncertain how to select these patients and what is the best timeline to offer early endovascular treatment (4, 5).

TO-ACT (Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis) is the first multicenter randomized clinical trial in severe CVST (6). Patients with radiologically confirmed CVST who had at least 1 risk factor for a poor outcome (mental status disorder, coma state, intracerebral hemorrhage, or thrombosis of the deep venous system) were included. A total of 67 patients were randomized to endovascular venous thrombectomy (EVT) with standard medical care (intervention group) vs. standard medical care alone (control group). The study found in functional outcome at 12 months between both groups (RR ratio, 0.99; 95% CI, 0.71–1.38). However, TO-ACT is underpowered and should not be interpreted as definitive proof that EVT is ineffective in CVST. Our patient did meet TO-ACT inclusion criteria with presence of ICH.

The INARI medical FlowTriever system is the only FDA approved mechanical thrombectomy system indicated for the treatment of pulmonary embolism. It is specifically designed for venous clots. It is composed of a trackable large bore

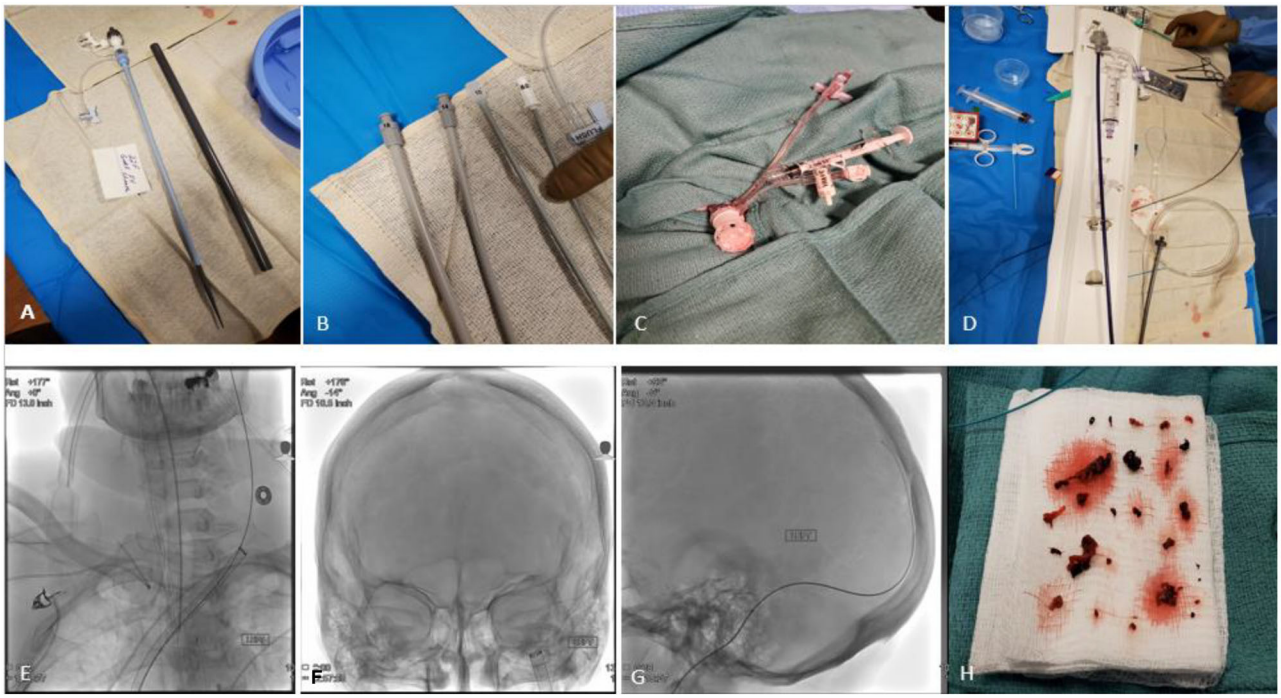

FIGURE 2 | Transvenous endovascular mechanical thrombectomy using the INARI FlowTriever system. **(A–C)** Right femoral venous access was obtained by placing a 22F GORE DrySeal Flex Introducer Sheath with pre-dilation using 8F, 10F, 14F then 18F dilators. 2 cc of air was inflated in the GORE DrySeal Flex valve to stop back flow of venous blood. **(D,E)** After selecting the left internal jugular vein; The INARI Triver20 large bore aspiration catheter was advanced with its dilator over the TAD2 exchange wire (Over-the-wire technique) and then the dilator was removed. **(F–H)** large volume venous clots retrieved using the Vect074 reperfusion catheter and Solitaire stent retriever and negative pressure applied with a 60 cc syringe through the INARI Triver20 large bore aspiration catheter. Anticoagulation with heparin was resumed after the procedure.

aspiration catheter; INARI Triver20 (available in other different sizes: Triver16: 16 French, Triver20: 20 French, and Triver24: 24 French), connected to a large volume syringe for manual aspiration designed to extract large volume of clots. The INARI FlowTriever Catheter; has 3 expanding nitinol mesh disks; available in 4 sizes: Small (6–10 mm), Medium (11–12 mm), (large 15–18 mm), and X large (19–25 mm), designed to engage and disrupt venous clots and subsequently deliver it to the large bore aspiration catheter. This FlowTriever size offers a larger diameter compared to other stentretrivers (Solitaire, Trevo) and might be more efficient to disrupt larger venous clots. However, this warrants further studies.

From a technical standpoint; It was feasible to advance the INARI FlowTriever system through the inferior vena cava, right atrium, superior vena cava, and into the left jugular bulb. However, we were unable to advance the Triever 20 aspiration catheter into the sigmoid sinus, even over the Vecta 071 while the solitaire device is deployed. The Triever 20 aspiration catheter and the flow triver is a bulky system. New changes has evolved in the Inari system. The Triever20 Curve has a customizable 260° bend designed for improved navigability and torqueability for challenging anatomy. The Triever24 comes now with FLEX technology to better navigate tortuous anatomies and smoothly deliver the catheter to the left pulmonary artery. These modifications might make it doable to track the Triever aspiration catheter distally into the sigmoid and transverse sinuses.

The 22 French (7.33 mm) venous access was sutured with figure of 8 technique. This was followed with manual pressure. No post-procedure groin complications noted. This illustrates that the common femoral vein can accommodate large catheters if needed (Common femoral vein approximate diameter is 8.2 ± 0.14 mm). In a multicenter, single-arm FLASH Registry evaluating real world patient outcomes after treatment of pulmonary embolism with FlowTriever; of the first 230 analyzed, there was a single case of access site complication (0.4%). There was 0% mortality throughout 48 h post-procedure, with 3 major bleeds (all non-ICH), and 0 intra-procedural device and procedure related adverse events (7).

In our patient; the angiographic results revealed partial recanalization and improvement of venous flow after extracting a large clot burden. MRI brain at 3-months follow up demonstrated near complete recanalization of the venous sinuses (**Figures 3**, **4**). Mechanical disruption of the venous clot in selected patients would probably decrease the intracranial pressure and give systemic medical anticoagulation (heparin drip, enoxaparin, novel oral anticoagulants) a better chance to stabilize and dissolve the clot.

Various neuro endovascular techniques has been attempted to treat cerebral venous sinus thrombosis. This includes direct

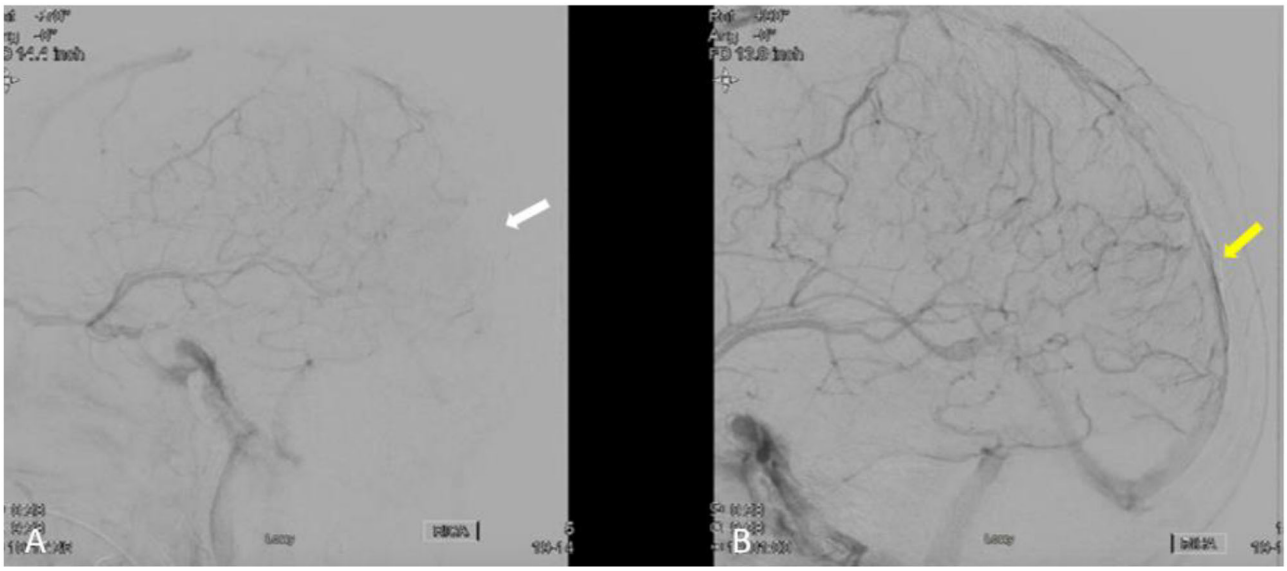

FIGURE 3 | (A,B) Lateral cerebral angiogram run in **(B)** is post venous thrombectomy treatment demonstrating partial recanalization of posterior aspect of superior sagittal sinus and left transverse, and sigmoid sinuses (yellow arrow) compared to pre-treatment (white arrow in **A**).

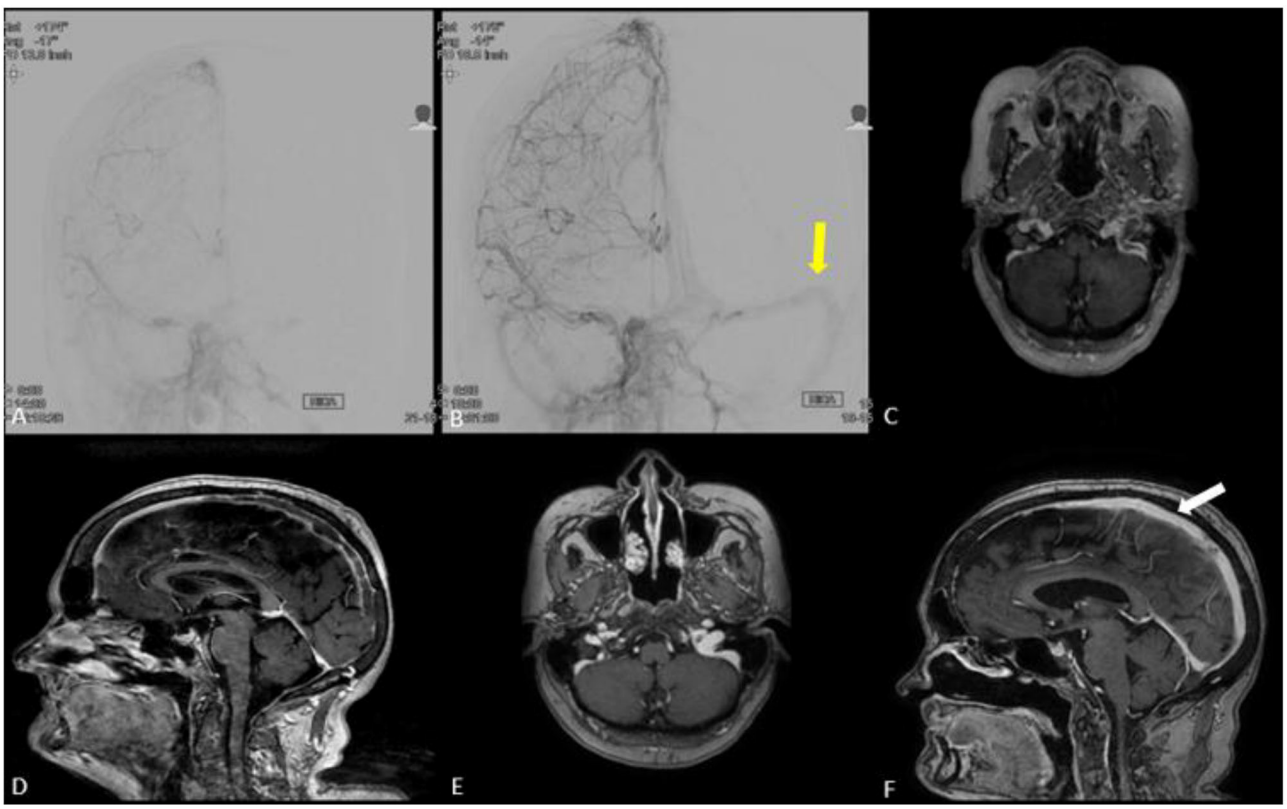

FIGURE 4 | (A,B) Anteroposterior cerebral angiogram run in **(B)** is post treatment demonstrating partial recanalization of posterior aspect of superior sagittal sinus and left transverse/sigmoid complex (yellow arrow) compared to pre-treatment **(A)**. **(C–F)** MRI brain with and without contrast in axial **(E)** and coronal views **(F)** demonstrating near complete recanalization of superior sagittal sinus (white arrow) and left transverse/sigmoid complex at 3 months clinic follow-up compared to MRI brain obtained prior to venous thrombectomy **(C,D)**.

aspiration thrombectomy, stent retriever thrombectomy, balloon thrombectomy, balloon angioplasty and stenting, AngioJet. However; it is unclear which approach and or devices provides the optimal restoration of venous blood flow; and further evidence is needed (8–10).

We believe that intracranial mechanical venous thrombectomy is still lacking behind compared endovascular thrombectomy for ischemic treatment. New innovations including catheters, stent retrievers, and procedure techniques is warranted to advance the field.

CONCLUSION

Current neuro endovascular techniques and devices are not particularly designed for treatment of cerebral venous sinus thrombosis pathology and there is utmost need for further innovation and new devices. This case report illustrates a transvenous endovascular treatment of cerebral venous sinus thrombosis with an off-label use of the INARI FlowTriever System. There was no peri-procedure complications noted with a good clinical functional outcome. Further data are required from this population of interest with severe CVST.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SB, NL, and OZ contributed to conception and design of the study. SA contributed to data analysis. SB and MK wrote the first draft of the manuscript. All authors contributed to manuscript revision.

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CASE REPORT
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Roadmap Guided Direct Percutaneous Vertebral Artery Puncture for Mechanical Thrombectomy of Acute Basilar Artery Occlusion: A Technical Case Report and Review of the Literature

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Access techniques for mechanical thrombectomy normally include percutaneous puncture of the common femoral or, more recently, the radial artery. Although target vessel catheterization may frequently not be devoid of difficulties *via* both routes, the vast majority of mechanical thrombectomy (MT) cases can be successfully managed. However, in a significant minority of cases, a stable target vessel access cannot be reached resulting in futile recanalization procedures and detrimental outcomes for the patients. As such, in analogy to direct carotid puncture for anterior circulation MT, direct vertebral artery (VA) puncture (DVP) is a direct cervical approach, which can constitute the only feasible access to the posterior circulation in highly selected cases. So far, due to the rarity of DVP, only anecdotal evidence from isolated case reports is available and this approach raises concerns with regard to safety issues, feasibility, and technical realization. We present a case in which bail-out access to the posterior circulation was successfully obtained through a roadmap-guided lateral direct puncture of the V2 segment of the cervical VA and give an overview of technical nuances of published DVP approaches for posterior circulation MT.

Keywords: mechanical thrombectomy (MT), direct vertebral puncture, stroke, large vessel occlusion, bail out

INTRODUCTION

Access techniques for mechanical thrombectomy normally include percutaneous puncture of the common femoral or, more recently, the radial artery. Although target vessel catheterization may frequently not be devoid of difficulties *via* both routes, the vast majority of mechanical thrombectomy (MT) cases can be successfully managed. However, in a significant minority of cases, a stable target vessel access cannot be reached resulting in futile recanalization procedures and detrimental outcomes for the patients (1). As such, in analogy to direct carotid puncture for

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CASE PRESENTATION

A 70-year-old female patient presented with a right-sided hemisyndrome and an NIHSS of 4 for 6 h in the emergency department in the morning. Clinical symptoms improved spontaneously before critically deteriorating suddenly at 7 p.m. the same day to a GCS of 6.

IMAGING

Imaging upon admission identified neither signs of acute ischemic stroke nor a detectable vessel occlusion. Imaging upon sudden clinical deterioration demonstrated early ischemic changes in the posterior cerebral artery (PCA) territories bilaterally and a basilar hyperdense artery sign. CT angiography (CTA) showed a distal basilar artery (BAO) occlusion, extending from the basilar tip into both proximal segments of the posterior cerebral arteries (PCA, P1 segment; **Figure 1D**). Regarding vascular access, a type three aortic arch, severe atherosclerosis of the supra-aortic vessels (**Figure 1A**), an occluded stent in the proximal common carotid artery (CCA) prolapsing into the aortic arch (**Figure 1B**), a direct take-off of the left severely long segmentally stenotic VA from the aortic arch immediately adjacent to the stent, and an osteal VA stenosis on the right with a steep-angled take-off from the subclavian artery were noted (**Figure 1C**).

TREATMENT

Clinical indication for treatment was based upon a patient's decree explicitly stating maximal therapy and according to the early time window considering the second event, treatment was pursued despite the patient's compromised clinical state. As intravenous thrombolysis was contraindicated due to neoplastic disease, the intubated patient was directly transported to the angiosuite for MT. Both groins were pulseless. Since the right femoral artery was knowingly occluded, a nine French sheath was placed in the nearly pulseless left common femoral artery (CFA) for access under ultrasound guidance. Despite the passage of tight stenosis in the left common iliac artery, catheterization of both vertebral arteries was unsuccessful during multiple attempts using various select catheters and wires. Thus, a right transradial approach to gain access to the right dominant VA with a six French radial sheath was undertaken. However, multiple selection attempts of the right VA remained futile due to the kinking of the middle segment of the subclavian artery as well as the steep-angled VA take-off and the ostial stenosis (**Figure 1**). As a bail-out access procedure, a direct percutaneous lateral cervical VA access was entertained considering the acute nature with a short time interval from clinical deterioration to groin puncture and overall dismal prognosis of persistent BAO. As in total 60 min had elapsed (30 min for femoral access and 30 min for radial access), the direct puncture was favored over a more time-consuming surgical cutdown. Under road mapping, *via* the right subclavian catheter injection, a micropuncture needle was percutaneously advanced from the far lateral cervical triangle at the height of C5 puncturing the lateral aspect of the C2 vertebral artery (**Figures 2A,B**). Following the return of arterialized blood, the microsheath was laced *via* the microwire and subsequently exchanged for a standard 10 cm 5F femoral sheath over a standard.038 steel exchange wire (**Figures 2C,D**). The operating access area for anatomical orientation of the V2 access is shown in **Figure 3A**. Persistent occlusion of the basilar tip and the right PCA (**Figure 3B**) was confirmed by direct vertebral sheath injection (**Figure 3B**). A five-French aspiration catheter (SOFIA) was wirelessly advanced up to the basilar embolus and a single aspiration maneuver (wADAPT technique) was performed (**Figure 3C**). The aspiration catheter remained obstructed by the thrombus and was removed under manual constant suction with combined parallel suction on the sheath, which itself became blocked upon removing the aspiration catheter. Control imaging *via* the subclavian catheter showed complete recanalization of the basilar tip and the PCA territories (TICI3; **Figure 3D**). The V2 segment demonstrated a contrast filling defect at the tip of the sheath representing residual thrombus. Despite prolonged and vigorous aspiration on the sheath it stayed blocked and no more thrombus could be retrieved. Thus, the sheath was removed under aspiration and manual compression was applied to the puncture site for 15 min. Control imaging *via* the subclavian catheter after manual compression as well as follow-up CTA after 24 h demonstrated no extravasation or pseudoaneurysm, persistent TICI 3 recanalization, and a residual wall adherent thrombus at the puncture site not impeding antegrade flow.

FOLLOW-UP IMAGING AND CLINICAL OUTCOME

The follow-up imaging done for 24 h has demonstrated extensive territorial infarctions in the right occipital lobe and pons, while CTA confirmed persistent complete recanalization, stable wall-adherent thrombus at the VA puncture site, and absence of a local dissection, pseudoaneurysm, or hematoma (**Figure 4**). Given the overall poor prognosis medical treatment was stopped in joint determination with the patient's family members and the patient expired.

DISCUSSION

Acute BAO accounts for about 1–4% of all acute ischemic strokes (AIS) with severe disability and mortality rates ranging

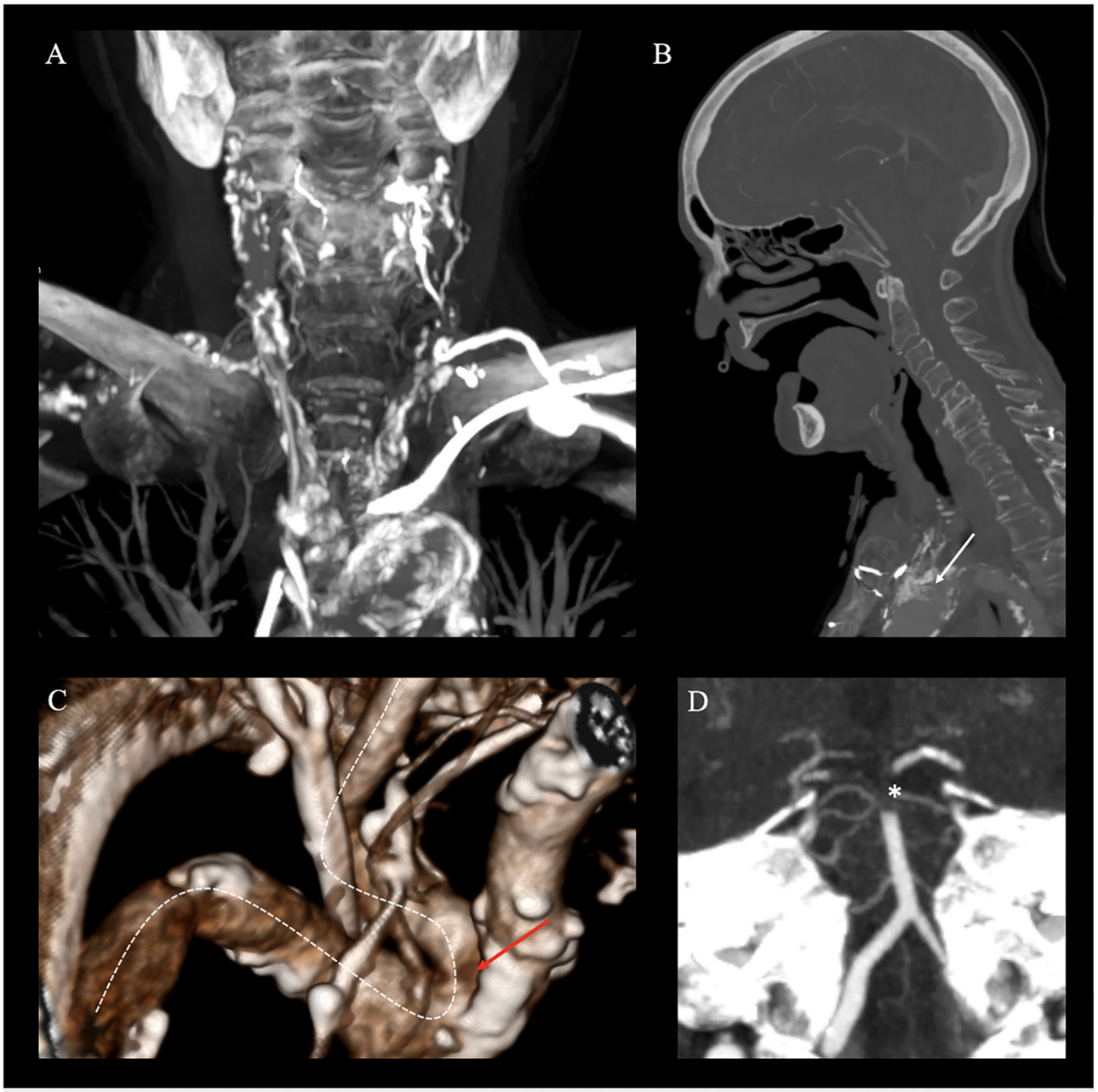

FIGURE 1 | Non-invasive emergency imaging. Emergency imaging of a 70-year-old female patient with acute basilary artery occlusion (BAO), on. **(A–D)** Computed Tomography Angiography (CTA) in MIP reconstruction shows severe atherosclerosis of the aorta and cervical arteries (coronal plane), **(A)** a prolapsing stent of the common carotid artery into the aortic arch (white arrow, sagittal plane), **(B)** kinking and stenosis of the right subclavian artery (white dotted line) and an osteal right VA stenosis on the right (red arrow) with a steep-angled take-off from the subclavian artery (white dotted line, 3D reconstruction), **(C)** and distal occlusion of the basilary artery extending to both P1 segments of the posterior cerebral artery [*; white star, paracoronal plane, **(D)**].

up to 86% (6). Substantial clinical evidence supports the clinical benefit of MT, which is currently considered the standard of care by most (7–10), althoughevidence from randomized-controlled trials (RCT) is lacking (11). According to the literature, a significant minority of interventions are unsuccessful in terms of vessel recanalization of (20%) and of this 17% due to the inability to reach the occlusion site (12). For these cases, rescue vascular access techniques, such as early direct carotid or vertebral puncture or surgical arterial access, should be considered on an individual basis (1).

According to the current standard of treatment, vascular access for MT is usually achieved by a femoral arterial puncture

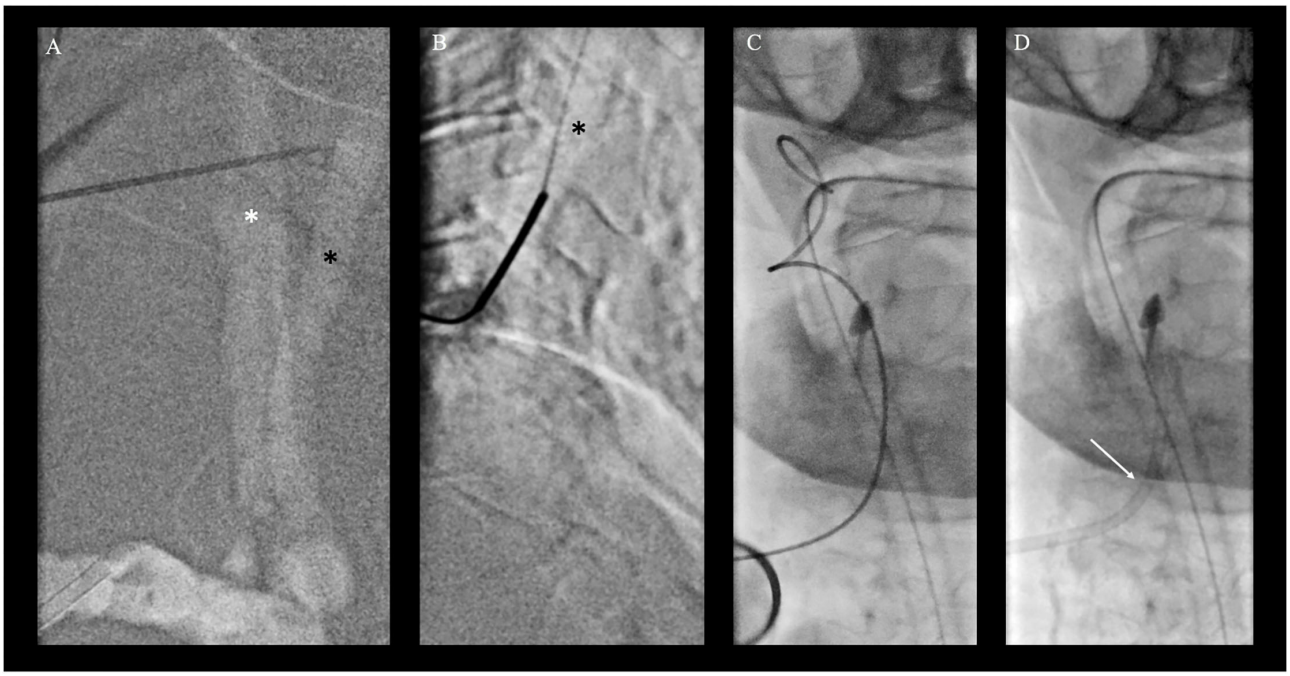

FIGURE 2 | Bailout direct cervical vertebral artery (VA) access. **(A)** Roadmap injection through the right radial artery shows right common carotid artery (*; white star) and dorsally located VA of the V2 segment (black arrow) in posterior-anterior projection with a puncture needle for better orientation. **(B)** Direct puncture of the V2 segment of the VA under roadmap guidance in lateral projection at the level of C4/5 of the cervical spine. The micropuncture needle was percutaneously advanced from the far lateral cervical triangle at the height of C5 puncturing the lateral aspect of the V2 vertebral artery at the C4/5 level. **(C, D)** Placement of a microsheath via the microwire **(C)** and subsequent exchange for a standard 10 cm 5F femoral sheath over a standard 0.038 steel exchange wire **(D)**.

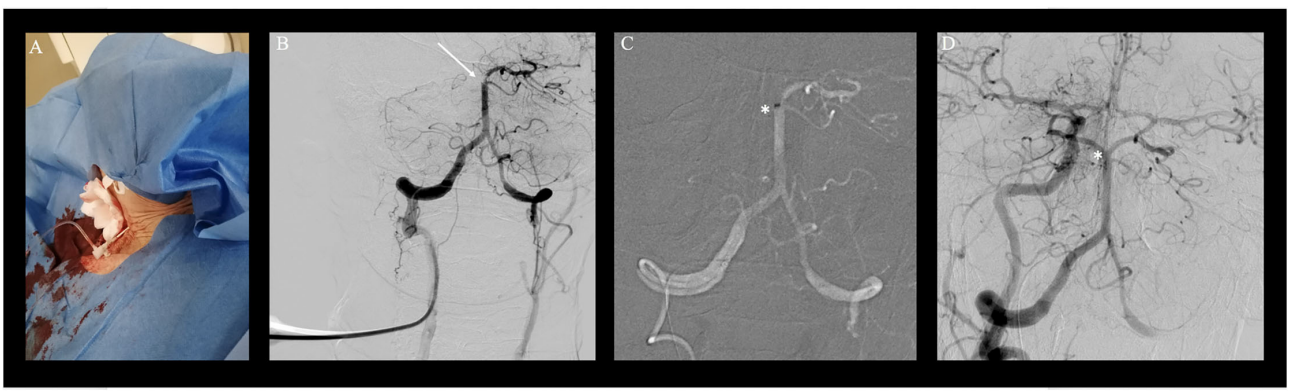

FIGURE 3 | Transvertebral mechanical thrombectomy for basilary artery occlusion (BAO). Transvertebral mechanical thrombectomy for basilary artery occlusion (BAO). **(A)** Access site of the patient with a femoral sheath in place after single wall percutaneous puncture of the right vertebral artery of the V2 segment at the level of C4/C5 of the cervical spine. **(B)** Transvertebral injection and documentation of persistent BAO and right posterior cerebral artery occlusion (white arrow). **(C)** Wireless navigation of the large bore aspiration catheter (SOFIA) up to the occlusion site (*; white star). **(D)** Control fluoroscopy via right brachial artery with full recanalization of the occlusion site (white star).

for catheterization of the supra-aortic vessels. Yet, severe vessel and aortic arch remodeling secondary to chronic hypertensive disease may hinder timely and successful selective catheterization of the target cervical vessel. Recently, evidence points to adopt a radial-first strategy for both diagnostic procedures and MT were increased, especially for BAO (13, 14). Yet, radial-first attempts may also remain unsuccessful in a small but important proportion of cases and some anatomies are likely to be problematic for both approaches (15, 16). In these highly selected cases, DVP may provide an elegant solution to quickly establish vascular access and provide a stable platform with the excellent transmission of torque and forces in relative proximity of the target vessel occlusion for subsequent MT of BAO.

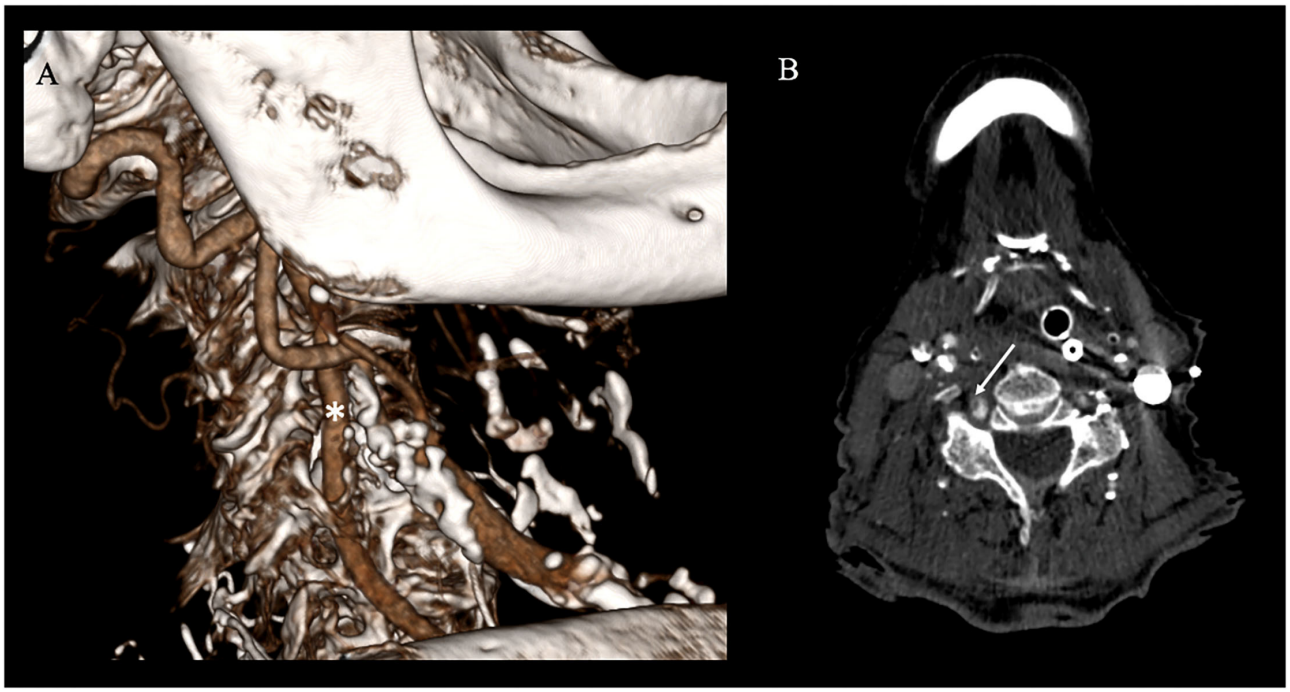

FIGURE 4 | Follow-up vascular imaging. **(A)** CT-angiography (CTA) with sagittal 3D-reconstruction shows continuous contrast filling of the vertebral artery (*; white star) and no vascular. **(B)** However axial CTA shows evidence of a residual wall adherent thrombus at the former access site section but no cervical hematoma (white arrow).

Direct VA puncture (DVP) has been performed under fluoroscopy, US and as of recently also under road mapping (2, 3). Percutaneous angiography of the vertebral artery was first described in 1950 by Lindgren (17) who stated that the examiner presses two fingers of the left hand in between the brachiocephalic vessels and the aerodigestive lumen, at the level of C4. A catheter needle is then introduced toward the midline until it touches the vertebral body and directed upward and outward until it glides between adjacent transverse processes to hit the vertebral artery. Lindgren's technique was further refined for diagnostic angiographies by Sjögren in 1953 and adapted in a similar approach during endovascular treatment of basilar tip aneurysms by Weill and Cognard et al. in 1998 (17). Over time, a variety of puncture sites and guidance strategies for DVP access have been described and were recently reviewed by Elhorany et al. (2). Their results underline that clinical evidence supporting different techniques of DVP for MT in the posterior circulation is extremely limited. Only four cases other than this one were reported in the context of MT for BAO, three describing access to the V3 segment (using ultrasound guidance or road mapping) and only one describing V2 access using ultrasound (2–5). Their image [**Figure 3**, (7)] these operators seem to have used a far lateral approach, too, although the puncture site has not been documented on the fluoroscopy image. While limited previous reports of endovascular access by direct percutaneous V2 puncture exist, they have only been described for aneurysm treatment *via* coiling (18). To the best of our knowledge, this is the first report of a direct percutaneous V2 puncture for MT of a BAO (2). We preferred roadmap guidance as we already had a catheter positioned in the proximal subclavian artery and were thus able to visualize both the carotid and the vertebral artery for guidance. The lateral approach offers more space for the operator and more degrees of freedom for the needle movement than the anterior approach, especially in the patients with short necks. Furthermore, the separated visibility of the VA from the CA when a lateral approach is chosen in comparison to ventral access argues in favor of this approach (17). As there is no dedicated material on the market for direct cervical punctures, we used a standard short femoral sheath in combination with a standard micropuncture kit. The puncture was straightforward as were the exchange maneuvers. Owing to the relative proximity of the sheath end and the embolus, wireless advancement of the aspiration catheter and subsequent direct aspiration maneuver were smooth and successful. Problems arose from the relatively small sheath that had been chosen as the thrombus was ultimately occluding the sheath. A larger sheath would have likely been advantageous in this respect. Yet, one has to weigh the benefits of a large sheath against the problems of puncture site closure. The possibility of vessel injuries, such as dissection, occlusion, distal embolism, arteriovenous fistula, and cervical compressive hematomas, as well as brachiocervical plexus nerve injury need to be critically considered, especially in a patient being on systemic thrombolytic, anticoagulation, or antiplatelet therapy. The authors Semeraro et al. and Blance et al. reported the use of a vascular closure system for DVP in their recently published case series to minimize the potential

TABLE 1 | Comparison of direct vertebral artery access techniques for mechanical thrombectomy in patients with acute basilary artery occlusion.

Author	Date of publication	Access technique	Vertebral segment	Access according to anatomical landmark	Puncture site treatment	Complications
Present case	-	Roadmap guided	V2	Posterolateral approach with needle introduced at the level of the process of C4 and C5	Manual compression	None
Elhorany et al. (2)	Jun 2020	Roadmap guided	V3	Posterolateral approach with needle introduced inferior to the tip of the mastoid process.	Manual compression	None
Semeraro et al. (3)	Jan 2021	Ultrasound-guided approach	V2	US probe placed oriented longitudinally to the V2, needle introduced between the transverse process of C4 and C5.	Vascular closure system (FemoSel, Terumo)	None
O'Reilly et al. (4)	Aug 2019	Ultrasound-guided approach	V3	US probe placed below the ipsilateral mastoid process, needle introduced proximal to the main collateral VA feeding branch	NA	None
Desai et al. (5)	March 2014	Ultrasound-guided approach	V3	US probe placed in the transverse orientation to the VA, needle introduced at the V3 segment inferior to the tip of the mastoid process.	NA	None

the US, ultrasound; V2, segment 2 of the vertebral artery segment 2; V3, segment 3 of the vertebral artery.

risk of cervical hematoma. In our case, 15 min of focal manual compression was efficient to achieve durable hemostasis (3, 19). A structured summary of the different DVP access techniques for MT in patients with acute BAO is given in **Table 1**. Alongside different DVP techniques, also surgical cutdowns have been proposed for direct VA access (20). In comparison, ultrasound- and/or roadmap-guided DVP of the V2 or V3 segment are less likely time-consuming and thus preferable. One could also consider leaving the sheath after the procedure and closing the arteriotomy surgically once the situation is less time-sensitive. Our presented technique is facilitated by the use of road mapping control which is able to localize precisely the target artery to be punctured. As most DVP procedures are likely for bail-out access in MT transradial or transfemoral diagnostic catheters are likely to be in a position to provide some sort of VA roadmap. Our report adds to the extremely limited direct VA access experience, describes a different technical nuance compared to similar approaches describes in the literature (2), and illustrates the procedure in detail, which might be of interest to physicians performing MT.

To conclude the DVP approach *via* roadmap-guided fluoroscopy may be a reasonable bail-out vascular access method for MT in patients with BAO in whom standard techniques remain futile. Prior road mapping of the targeted artery *via* femoral or radial approach may allow for straightforward fluoroscopy-guided cervical VA puncture and effective vessel recanalization in otherwise impossible cases. The size of the sheath and potential complications of this access must be considered and weighed against the natural history of the disease aimed to treat. Although our patient did not fare well in the end, it is fair to state that DVP did not attribute to this outcome.

TAKE-HOME MESSAGES

- Direct percutaneous puncture (DVP) of the VA appears to be a valuable rescue access strategy for MT in patients with BAO when standard access techniques fail.
- The V2 segment of the VA can be directly punctured by a lateral cervical approach.
- Direct VA puncture (DVP) can be facilitated by roadmap guidance.
- The material commonly employed for transfemoral access can be successfully used in DVP.
- Safety aspects of this technique must be considered and weighed against the natural history of the disease aimed to treat.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JN and ES: study design, acquisition of data, image processing, image analysis, data analysis, statistical analysis, and drafting the manuscript and revising it critically. GB: data analysis and drafting the manuscript and revising it critically. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Treatment and Postinterventional Management of a Fusiform Intracranial Aneurysm in a Professional Soccer Player: A Case Report

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Introduction: While intracranial aneurysms are common lesions affecting between 1 and 5% of the general population, the prevalence in professional athletes remains unknown. The result is uncertainty and lack of guidelines on appropriate treatment of these patients.

Case Presentation: A 29-year-old professional soccer player presented in our hospital with an incidentally found intracranial aneurysm. After detailed depiction of the aneurysm and interdisciplinary discussion, endovascular treatment using a flow diverter was chosen to be the best treatment modality. Postinterventional medication consisted of dual antiplatelet therapy with aspirin and clopidogrel. The main challenge in managing the case of our patient was the combination of the dual antiplatelet treatment regime with his professional career in a contact sport.

Conclusion: Due to lack of literature or similar reports regarding the management of professional athletes with intracranial aneurysms, the optimal treatment strategy remains unclear. Even though decisions should be made dynamically and case-adapted to each situation, developing a registry could help provide guidance and new ideas for similar cases in the future.

Keywords: intracranial aneurysms, professional athletes, endovascular treatment, dual antiplatelet therapy, case report

BACKGROUND

Intracranial aneurysms are common lesions affecting between 1 and 5% of the population, irrespective of ethnicity, or geographical location (1). There exists a considerable body of literature on the prevalence, diagnosis, and management of intracranial aneurysms in the general population, but there exist no studies that assessed the prevalence in professional athletes. The result is uncertainty and lack of guidelines on appropriate treatment, especially in terms of adjunctive antiplatelet treatment in cases of stent-assisted or flow diverter treatment and contact sports.

Formation of intracranial aneurysms is an incompletely understood, complex interplay between genetic and environmental risk factors. Hemodynamic stress and vascular risk factors, such as hypertension, lipid accumulation, arteriosclerosis, and smoking, are known to contribute to the formation of aneurysms in the second half of life. On the contrary, vascular risk factors do not seem to influence the development of aneurysms in younger patients. Therefore, conditions such as polycystic kidney disease, fibromuscular dysplasia, and connective tissue disorders have to be considered (1). The role of traumatic events, especially in athletes, should not be underestimated in the formation of intracranial aneurysms. A number of activities and mechanisms are known to potentially result in traumatic intracranial aneurysm (TICA), including blunt head trauma, which typically occurs during sports like soccer (2). Given the high intensity of the sport and acceleration forces to the brain and vessels while "heading the ball," it seems evident that soccer carries an inherent risk of head injuries with possible consequences such as TICA. In the majority of cases, these injuries are the result of unexpected or unintentional contact with other players or the playing surface (3).

Here, we report the case of a professional soccer player who presented with an incidentally found intracranial aneurysm, and discuss our considerations regarding treatment, postinterventional medication, and his career.

CASE PRESENTATION

In August 2019, while trying to head a ball, a 29-year-old professional soccer player sustained a concussion while colliding with another player. On arrival in the emergency room, the patient presented with retrograde amnesia and a Glasgow Coma Scale (GCS) 15 without any focal neurological deficits. Neuroradiologists suspected a traumatic subarachnoidal hemorrhage on computed tomography (CT) scans, confined to the Sylvian fissure (**Figure 1A**). Further imaging with magnetic resonance imaging (MRI) was recommended and showed a 10 × 6 × 5 mm fusiform aneurysm of the right middle cerebral artery (MCA), located in the distal M2-segment (**Figure 1B**). For exact depiction of the incidental aneurysm and assessment of treatment options, cerebral angiograms were acquired (**Figures 1C,D**). After interdisciplinary discussion, endovascular treatment using a FRED Jr. flow diverter (2.5 × 20 × 25 mm) was chosen to be the best treatment modality. The procedure was performed by the end of August 2019 (**Figure 2**), and the patient recovered uneventfully. Postinterventional medication consisted of dual antiplatelet therapy with aspirin 100 mg per day and clopidogrel 75 mg per day. In February 2020, in order to be cleared for contact drills and regular games, we stopped clopidogrel therapy. A few days after changing to monotherapy with aspirin, he presented to the emergency department with progressive headache, nausea, and vomiting. Clinical examination revealed no focal neurological deficits and a GCS of 15. Brain MRI indicated nearly complete thrombosis of the aneurysm (**Figure 3A**). Slow-flow was depicted in an MCA side branch (**Figure 3B**), originating from the aneurysm-wall, with a perfusion deficit of the respective territory (**Figure 3C**) and small embolic lesions on diffusion-weighted imaging (DWI, **Figure 3D**). Therefore, we decided to restart the dual antiplatelet therapy until the next follow-up 1 month later, and limit sport activities to non-contact drills. The follow-up MRI scan showed no new cerebral infarction (**Figure 3E**) and normalization of the flow in the MCA side branch. After consulting with our neurologists, we continued with clopidogrel monotherapy (75 mg per day), stopped aspirin, and cleared the patient for professional games. Six-month follow-up MRI scan showed complete occlusion of the aneurysm (**Figure 3F**), regular flow in the side branch, and no cerebral infarction in the MCA territory or any hemorrhages. The patient is currently participating in soccer practice and games without any problems.

Abbreviations: TICA, traumatic intracranial aneurysm; GCS, Glasgow Coma Scale; CT, computed tomography; MRI, magnetic resonance imaging; MCA, middle cerebral artery; VRT, volume-rendering technique; DWI, diffusion-weighted imaging.

DISCUSSION AND CONCLUSION

After the detection of an unruptured intracranial aneurysm, various factors have to be considered to identify the ideal management. In general, there are three options to treat intracranial aneurysms: craniotomy with clip ligation, endovascular approaches, and observation. Incidentally discovered aneurysms are usually observed or treated electively, depending on the size and location of the aneurysm as well as patient-related factors, such as age, health, and professional conditions (4). Selecting the best treatment modality is even more difficult in professional athletes, among other things, because of lack of medical literature for guidance on appropriate postinterventional medication in cases of flow diverter implantation.

In our case, the best option was considered to be treatment with a mini flow diverter, which features the necessity of adjunctive antiplatelet medication. The same medication regimen applies to stent-assisted endovascular treatment, which represents a disadvantage of these two strategies because of the distal location and fusiform nature of the aneurysm. Alternatives of clip ligation and coiling were interdisciplinary discussed because of their advantage of not necessitating antiplatelet medication but were not feasible in our patient's case because of the fusiform nature of the aneurysm and its localization within the Sylvian fissure.

The main challenge in managing the case of our patient was the combination of aspirin and clopidogrel with his professional career in a contact sport. With flow diverter-treated intracranial aneurysms, it is impossible to omit antiplatelet drugs periinterventionally. Lacking established guidelines, individualized, case-adapted decisions had to be taken in the following months. We aimed at enabling monotherapy as soon as possible while simultaneously ensuring high-enough antithrombotic drug activity to clear him for games and contact

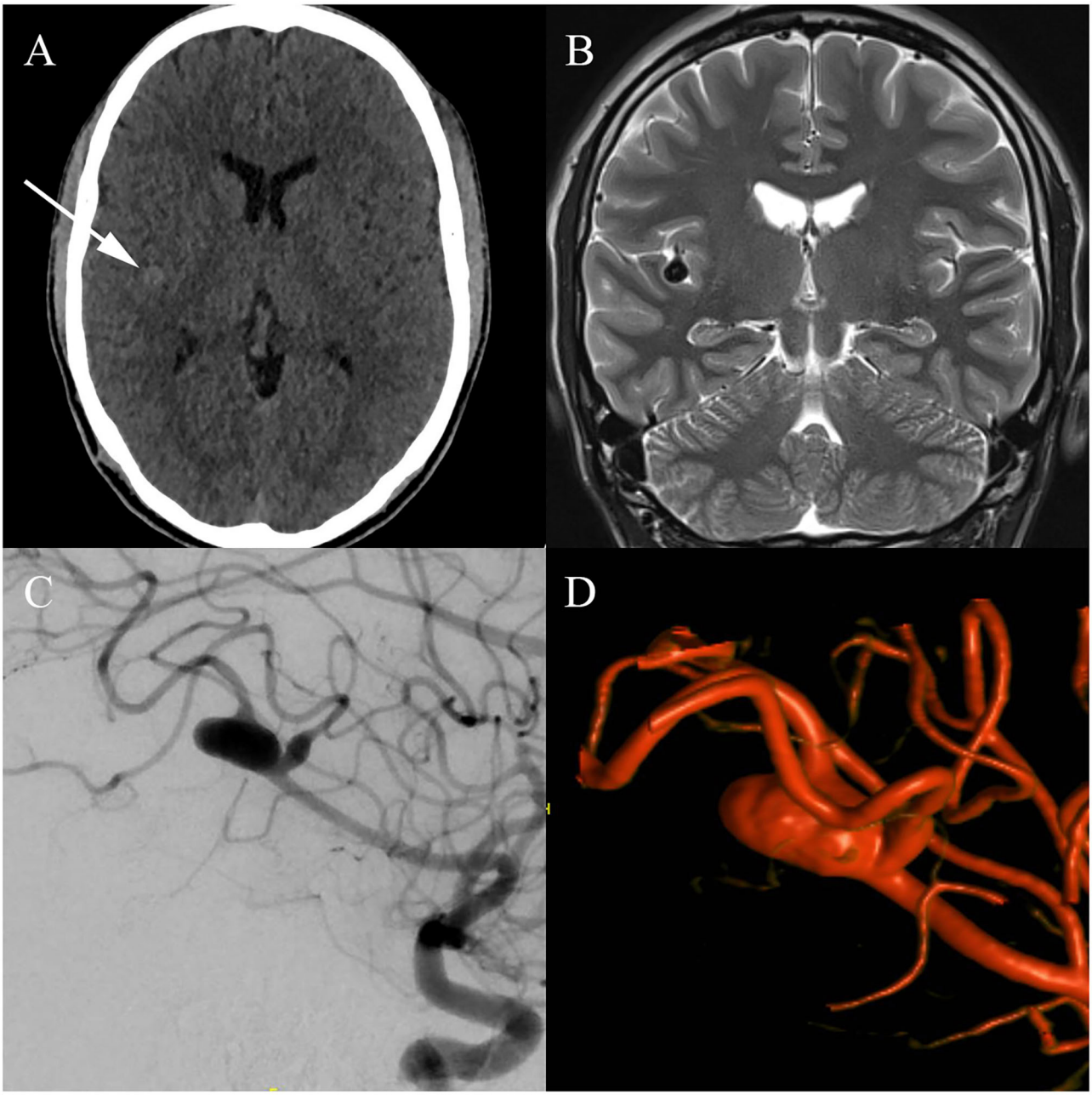

FIGURE 1 | Initial imaging findings: **(A)** Initial computed tomography (CT) images reveal a hyperdense structure confined to the right Sylvian fissure, leading to further investigation with magnetic resonance imaging (MRI). **(B)** T2-weighted MRI images do not confirm the suspected hemorrhage; instead, a fusiform aneurysm located in the distal M2-segment of the right middle cerebral artery (MCA) is delineated. **(C)** Cerebral angiogram illustrates a fusiform aneurysm, located in the inferior trunk of the right MCA. Furthermore, fusiform dilatation of a parieto-occipital branch arising from the right MCA is seen. The lesions are located adjacent to the right insula, in the depth of the Sylvian fissure. **(D)** Three-dimensional volume-rendering technique (VRT) of the aneurysm.

drills. As we used a small flow diverter in a distal vessel, we deemed it reasonable to sustain the dual antiplatelet therapy for 6 months and then continue with the aspirin monotherapy, independent of the profession of our patient. However, after experiencing a perfusion deficit and slow flow in the aneurysm side branch, the dual antiplatelet therapy was reinstated for 1 more month. After 4 weeks, and in order to clear the patient for games, we tried a different monotherapy regimen, this time with clopidogrel. The hypothesis was that clopidogrel alone would feature higher potency in terms of preventing arterial thrombosis compared to aspirin monotherapy. This plan was successful, as the patient could participate in games without

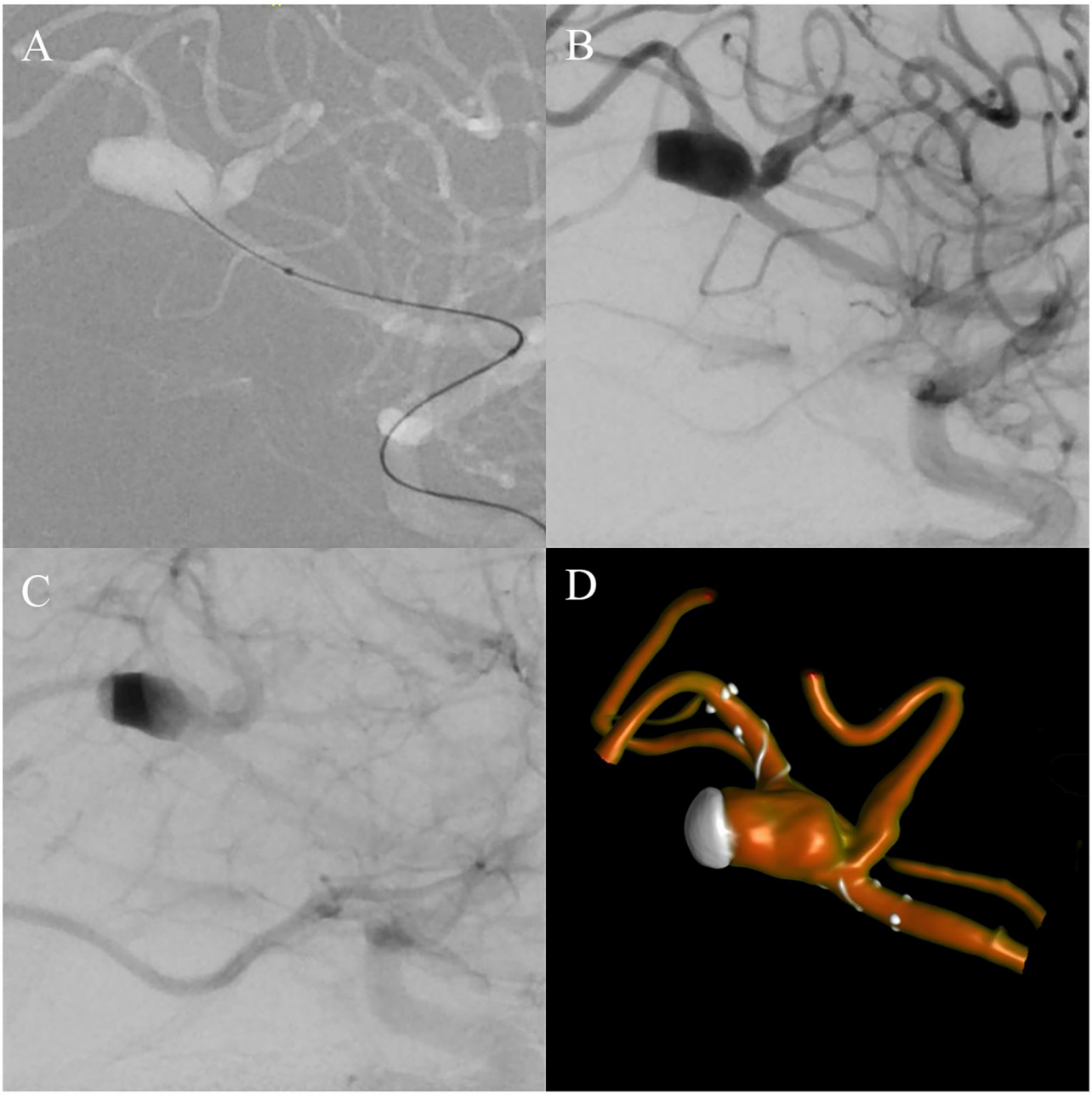

FIGURE 2 | Intra-interventional cerebral angiograms: **(A)** Lateral working projection during navigation of the microcatheter and microwire toward the aneurysm. **(B)** Directly after implantation of the flow diverter, contrast media stasis can be seen at the dome of the aneurysm as a gray, subtracted cap in the arterial phase. **(C)** In the venous phase, additional stasis in the majority of the aneurysm sack is depicted as a black band. **(D)** Postinterventional three-dimensional VRT showing the positioning of the flow diverter in relation to the aneurysm and marked stasis of contrast medium at the dome of the aneurysm.

any hemorrhagic complications, and we did not observe any infarctions or slow flow in the side branch in follow-up imaging. Our main concern was to not let our patient participate in soccer practice and games as long as he is under the dual antiplatelet therapy.

Regarding the formation of the aneurysm in our patient, it is unlikely that vascular risk factors, such as hypertension, lipid accumulation, and arteriosclerosis, contributed to the process. Conditions known to be associated with intracranial aneurysms in young patients, such as fibromuscular dysplasia, were evaluated and ruled out. Trauma-associated head and brain injuries, especially repetitive trauma, can result in hemorrhages, edema, alterations in cerebral blood flow, vasospasm, dissection, blood brain barrier disruption, chronic inflammation, and vessel

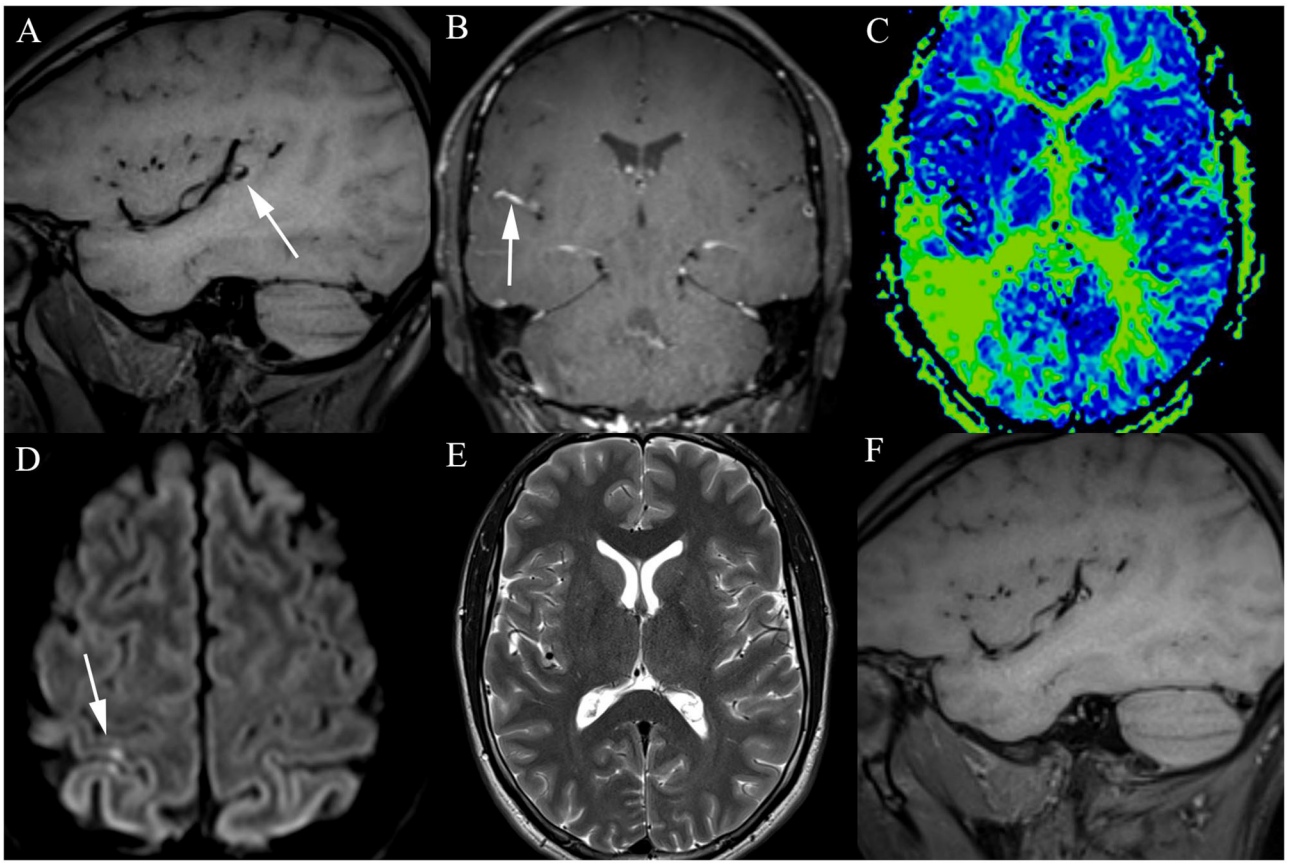

FIGURE 3 | Postinterventional imaging findings: **(A)** T1-weighted image 6 months after flow diverter implantation showing hyperintense thrombotic material around the flow diverter and near-complete occlusion of the aneurysm. The initial severe stasis at the dome (**Figure 2B**) is depicted as a hypointense cap. **(B)** Slow flow in the side branch originating from the aneurysm wall is documented 6 months post intervention after changing to monotherapy with aspirin. **(C)** Perfusion deficit of the affected territory is visible on mean transit time reconstructions of the MRI perfusion. **(D)** Small ischemic lesions, located in the right superior parietal lobule, are seen on DWI. **(E)** One month after detection of the slow flow in the side branch of the aneurysm-wall, T2-weighted images did not reveal an infarction in areas with delayed perfusion. **(F)** As 12 month-follow-up MRIs reveal, the aneurysm is completely filled with a hyperintense thrombotic material, which means that full occlusion of the aneurysm was achieved.

wall degeneration, which in turn can facilitate the formation of aneurysms (5, 6). The traumatic event that caused the presenting concussion in our patient was not related to the aneurysm, as we did not observe any intramural hematoma on initial MRI. Regarding the shape of the aneurysm, a mycotic aneurysm could be considered, as these aneurysms are defined by wall dilatation due to infection. However, the risk is higher in immune-compromised hosts; therefore, the pathophysiology of mycotic aneurysms does not match the history of our patient (7). The actual origin of the aneurysm of our patient remains unclear, but the most likely etiology is due to repetitive blunt head injuries during soccer practice and games, leading to a dissecting aneurysm that grew over time and took the final form we observed in August 2019.

Beyond medical considerations, public relations and financial aspects may affect the final decision in the treatment of aneurysms in professional athletes. While we, as physicians, base our decisions on medical evidence and literature, other aspects such as financial circumstances, the situation, or the wish of the athlete or the soccer club may influence the final decision of the patient. The case of our patient was complicated by the fact that his aneurysm was incidentally detected during his contract year. Therefore, while choosing a prompt treatment of the aneurysm, he also asked for the option to be cleared for games and contact drills as soon as possible.

During the last few years, newer surface-coated flow diverters, which limit the thrombotic potential of stents, have emerged. These surface-modified devices are ideally used for ruptured dissecting aneurysms but could also be useful in cases like ours. They may not require dual antiplatelet therapy and could be combined with monotherapy and continuous testing for antithrombotic drug activity. Hence, this approach could allow professional athletes to start with contact drills and games soon after the interventional procedure (8, 9).

We present the rare case of a professional soccer player, diagnosed with a fusiform MCA aneurysm, necessitating treatment with a flow diverter and subsequent dual antiplatelet medication. The history of our patient is, therefore, noteworthy in view of lacking literature or similar reports regarding the management of professional athletes under these circumstances. The situation becomes even more complex when the athlete wishes to continue his career despite the need for antiplatelet medication after endovascular aneurysm treatment. Developing a registry of professional athletes requiring antiplatelet medication, or even anticoagulation, could help to provide guidance and promote new ideas for similar cases in the future. Since the management of this case was successful, we wanted to provide advice and ideas on case-adapted decision-making for similar cases in the future. On a final note, we can say that decisions in these cases should be made dynamically and case-adapted to the situation, as there are more than the medical aspects at play in this arena.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

ME: data acquisition and drafting the manuscript. LB, IT, GH, KB, and RG: revision of the manuscript. M-NP: data interpretation, supervision, and critical revision of the manuscript. All authors read and approved the final version of the manuscript.

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The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2021.732640/full#supplementary-material

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CASE REPORT
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Mechanical Thrombectomy for M1 Subocclusive Thrombus With Lateral Lenticulostriate Artery Occlusion: A Case Report and Literature Review

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The treatment for middle cerebral artery subocclusive thrombi is not standardized. Here, we report a case of M1 subocclusive thrombus with lateral lenticulostriate artery occlusion that was successfully treated with mechanical thrombectomy. This article describes a treatment strategy for M1 subocclusive thrombus, focusing on the indications for mechanical thrombectomy. A 58-year-old male on admission for pneumonia had a sudden onset of dysarthria and motor deficits. He has a history of dilated cardiomyopathy and underwent left ventricular assist device implantation 3 years ago. At onset, his National Institutes of Health Stroke Scale (NIHSS) score was nine. Computed tomography angiography demonstrated a filling defect in the distal right M1 segment of the middle cerebral artery. Angiography confirmed the presence of a subocclusive thrombus within the distal right M1 segment, although peripheral blood flow was maintained. Mechanical thrombectomy was performed for the M1 subocclusive thrombus using a direct aspiration first-pass technique, resulting in successful aspiration of the thrombus on the first pass. After the procedure, recanalization of the lateral lenticulostriate artery was detected, and the patient demonstrated full recovery (NIHSS score 0). Mechanical thrombectomy can be considered as a treatment option in cases of acute ischemic stroke caused by M1 subocclusive thrombus with lateral lenticulostriate artery occlusion, which presents with a high NIHSS score or neurological deterioration.

Keywords: subocclusion, mechanical thrombectomy, ischemic stroke, middle cerebral artery, lenticulostriate artery

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INTRODUCTION

In contrast to complete occlusion, incomplete thrombotic vessel obstruction is called subocclusive thrombus or intraluminal non-occlusive free-floating thrombus (1). The internal carotid artery (ICA) is reportedly the most common location of subocclusive thrombus in the cervicocephalic arteries (2). However, literature describing middle cerebral artery (MCA) subocclusive thrombi is limited. While these thrombi can cause infarction, they are sometimes asymptomatic. Thus, the optimal treatment for subocclusive thrombi is still undefined. Here, we present a case of MCA subocclusive thrombus in the distal M1 segment with lateral lenticulostriate artery occlusion, for which mechanical thrombectomy was successful. Additionally, we propose a treatment strategy for suspected M1 subocclusive thrombus, with a literature review focusing on the indications for mechanical thrombectomy.

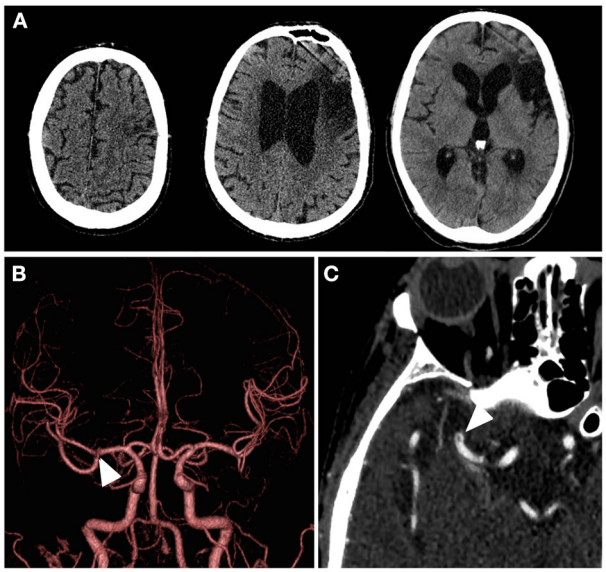

FIGURE 1 | Patient's cerebral imaging at the time of symptom onset. **(A)** Computed tomography showed an obsolete infarction of the left frontal lobe, but there were no findings suggestive of hemorrhage or acute infarction on the diseased side. **(B)** Computed tomography angiography with three-dimensional volume rendering did not exhibit obvious filling defects, but a localized microstenosis was noted in the right middle cerebral artery distal M1 segment (white arrowhead). **(C)** Subocclusive thrombus in the right middle cerebral artery distal M1 segment (white arrowhead) was found on close observation through the axial image of the computed tomography angiography with maximum intensity projection.

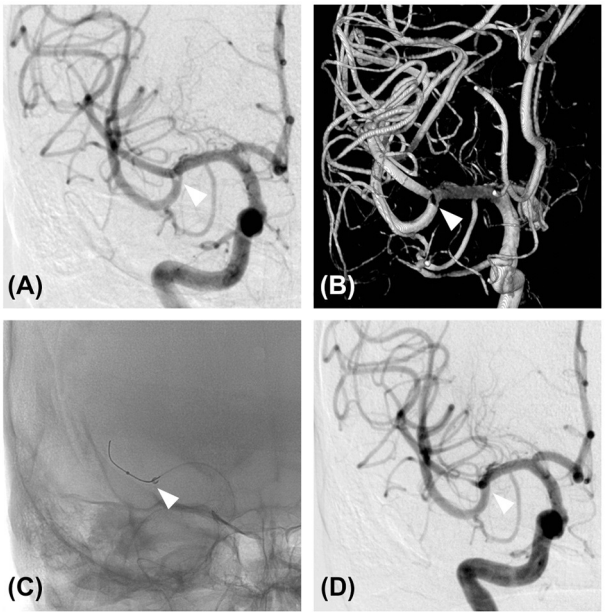

FIGURE 2 | Diagnostic angiography and mechanical thrombectomy. **(A)** Cerebral angiography of the right internal carotid artery showing an M1 subocclusive thrombus (white arrowhead). **(B)** Three-dimensional reconstruction of the cerebral angiography of the right internal carotid artery also showed the presence of a thrombus (white arrowhead). **(C)** Mechanical thrombectomy was performed using a direct aspiration first-pass technique. An aspiration catheter was advanced to the location of the thrombus (white arrowhead) with the aid of a microcatheter and a micro guidewire. **(D)** Cerebral angiography of the right internal carotid artery after the first pass. Note the complete removal of the thrombus (white arrowhead).

CASE DESCRIPTION

A 58-year-old male presented with a history of dilated cardiomyopathy. Three years ago, he had a left ventricular assist device (LVAD) implanted due to severe chronic heart failure. He had been taking warfarin to prevent thrombus formation in the LVAD circuit. He had a history of brain infarction, but with no neurological deficit and was listed for a heart transplant.

The patient had a sudden-onset dysarthria and left hemiparesis while on admission for pneumonia. On neurological examination, his National Institutes of Health Stroke Scale (NIHSS) score was nine (facial palsy, one; left arm motor, four; left leg motor, three; dysarthria, one). Computed tomography (CT) showed an old cerebral infarction of the left frontal lobe, and no other new lesions that explain his symptoms had been noted (**Figure 1A**). Although CT angiography (CTA) did not demonstrate complete occlusion of the right MCA (**Figure 1B**), a localized microstenosis and a filling defect in the distal M1 segment of the MCA were identified on careful observation (**Figures 1B,C**).

The patient exhibited elevated prothrombin time international normalized ratio (PT-INR) at 3.31; therefore, he was not treated with either intravenous tissue plasminogen activator (tPA) or additional antithrombotic medication. For a definitive diagnosis, we decided to perform a cerebral angiography and mechanical thrombectomy. Right internal carotid angiography revealed the presence of a subocclusive thrombus within the distal M1 segment (**Figures 2A,B**). Considering that the chance for a heart transplant will become lower if the neurological deficit persists, mechanical thrombectomy for the subocclusive thrombus was performed.

The treatment was performed under local anesthesia without heparinization. Through femoral access with a 9-French long sheath, a 9 Fr Optimo balloon guiding catheter (Tokai Medical Products, Inc., Aichi, Japan) was placed into the ICA, and a Penumbra 5MAX ACE 60 reperfusion catheter (Penumbra, Alameda, CA, USA) was advanced into the thrombus within the distal right M1 segment over a coaxially inserted Phenom 27 microcatheter (Medtronic, Minneapolis, MN, USA) and CHIKAI black 14 soft tip micro guidewire (Asahi Intecc, Nagoya, Aichi, Japan). Mechanical thrombectomy was performed for subocclusive thrombus using a direct aspiration first-pass (ADAPT) technique (**Figure 2C**). Complete removal of the thrombus without distal migration (**Figure 2D**) and recanalization of the lateral lenticulostriate artery (LSA) was confirmed (**Figures 3A–D**), resulting in successful aspiration on the first pass. Immediately after the recanalization, there was complete recovery of his left hemiparesis. After mechanical thrombectomy, the narrowing of the M2 segment of the MCA was noted. Since the diameter of the blood vessels showed

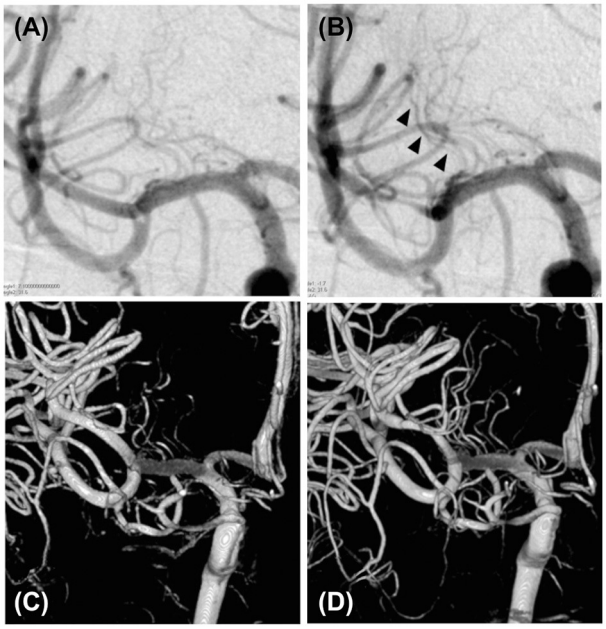

FIGURE 3 | Visualization of the lateral lenticulostriate artery before and after the mechanical thrombectomy. **(A)** Cerebral angiography of the right internal carotid artery showing a suspected poor lateral lenticulostriate artery appearance before mechanical thrombectomy. **(B)** Cerebral angiography of the right internal carotid artery showing recanalization of the thrombus after mechanical thrombectomy (black arrowhead). **(C)** Three-dimensional reconstruction of the lateral lenticulostriate artery from the cerebral angiography of the right internal carotid artery, showing a poor appearance of the lateral lenticulostriate artery before the mechanical thrombectomy. **(D)** Three-dimensional reconstruction of the lateral lenticulostriate artery from the cerebral angiography of the right internal carotid artery showing improved lateral lenticulostriate artery appearance after mechanical thrombectomy.

improvement over time compared to their original state, we concluded that the narrowing was spasm due to advancement of the tip of the aspiration catheter into the M2 superior trunk. The onset to picture time, picture to puncture time, and puncture to reperfusion time were 120, 60, and 40 min, respectively. Follow-up CT showed no hemorrhage or new ischemic lesion after the procedure. His postoperative NIHSS score was zero, and was discharged without any complications.

DISCUSSION

This report describes a case of M1 subocclusive thrombus with LSA occlusion that was successfully treated by mechanical thrombectomy. Most M1 subocclusive thrombi are treated conservatively. Moreover, through a literature search, we found only one case report of an M1 subocclusive thrombus (3). To date, there are no studies that have discussed the indications for mechanical thrombectomy in M1 subocclusive thrombus and its difficulty to diagnose.

Puetz et al. (4) reported that in 865 acute stroke and TIA cases evaluated by CTA, 10 cases (1.2%) had M1 subocclusive thrombi. This suggests that M1 subocclusive thrombus is not a rare condition. In previous reports (1, 3–5), the final diagnosis of M1 subocclusive thrombus was made using CTA or angiography. M1 subocclusive thrombi could be missed by magnetic resonance angiopgraphy (MRA) alone and may be diagnosed as lacunar infarction or branch atheromatous disease (BAD) (6). The neurological findings of lacunar infarction and BAD are reported to be relatively mild, with an NIHSS score of $\leq$7 and $\leq$5 for lacunar infarction (7) and BAD on admission, respectively. If the intracranial main artery has stenosis or occlusion, causing the symptom to be unclear on MRA despite a high NIHSS, CTA should be performed to investigate the subocclusive thrombi.

We reviewed the literature on conservative treatment for M1 subocclusive thrombi. To our knowledge, there are three reports describing 15 cases of M1 subocclusive thrombi with conservative treatment (1, 4, 5). Among these patients, nine (60%) presented with an NIHSS score of $\leq$4 points at the time of admission, and seven were discharged with an mRS score of $\leq$2. However, the two remaining patients exhibited neurological deterioration with poor prognosis (mRS of $\geq$3). In total, four patients (27%) had a poor prognosis. These findings suggest that conservative treatment usually leads to patient recovery. However, conservative management is insufficient when the presenting symptoms are severe or aggravated. In the case reported by Ohbuchi et al., medical management including intravenous tPA could not stop the neurological deterioration, hence mechanical thrombectomy was performed (3). There may be potential cases in which thrombectomy can be considered aggressively for patients with severe symptoms over refractory to conservative management.

An LSA recanalization was confirmed after the procedure in both the previous reports (3) and in our case. This suggests the effectiveness of LSA recanalization on M1 subocclusive thrombi, which may improve the functional prognosis of patients. Good LSA visualization after thrombectomy reportedly has a good functional prognosis for M1 complete occlusion (8). An LSA ischemia causes neurological deterioration (9), and the perfused area of the LSA has poor collateral circulation from other vessels, leading to early ischemia (10). Therefore, early reperfusion is desirable for LSA occlusion. In considering thrombectomy for M1 subocclusive thrombi, it may be useful to focus on the appearance of LSA.

Of note, our patient was on LVAD, a mechanical circulatory support device transplanted in patients with refractory heart failure awaiting heart transplantation (11). Although LVAD implantation improves prognosis and quality of life for a period of time (12), this device is a risk factor of hemorrhagic and ischemic stroke (13). For large vessel occlusion with patients on LVAD, mechanical thrombectomy can be performed safely and effectively (14, 15). We performed mechanical thrombectomy using ADAPT technique with a relatively low risk of perforation and postoperative hemorrhage (16). Due to the LVAD, MRI was contraindicated in this patient, which is a major limitation of this case report. It might be difficult to recognize small ischemic lesions postoperatively with only CT.

Therefore, mechanical thrombectomy can be considered for M1 subocclusive thrombi, especially in patients with a

high NIHSS score or neurological deterioration resistant to conservative treatment. Additionally, LSA visualization may be an important factor in decision-making. Nevertheless, our study is limited by a lack of case series data. Further research is needed to determine an optimal treatment strategy for this condition.

CONCLUSION

Based on our findings, mechanical thrombectomy can be a useful treatment option for selected cases of acute ischemic stroke caused by M1 subocclusive thrombus with LSA occlusion, which presents with a high NIHSS score or neurological deterioration.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

HY and SK: conceptualization, formal analysis, and investigation. HY: methodology, data curation, writing—original draft preparation, and visualization. SM, SK, and NS: validation, writing—review and editing, and supervision. SK: resources and project administration. All authors have read and agreed to the published version of the manuscript.

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Drug-Coated Balloon for the Treatment of Nonacute Symptomatic Intracranial Carotid Artery Terminus Occlusion: Initial Experience and Follow-Up Outcome

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Background: Studies on the recanalization for occlusion of the internal carotid artery terminus are scattered. Recently, drug-coated balloon (DCB) has been increasingly applied in the intracranial artery occlusion and achieved encouraging results. However, there seems no convincing data for the nonacute symptomatic internal carotid artery terminus occlusion (sICATO).

Objective: To assess the feasibility and effectiveness (safety) of DCB for patients with nonacute sICATO refractory to medical therapy.

Approach: This study included 30 patients with nonacute sICATO treated with DCBs and/or remedial stenting. The rate of successful recanalization, periprocedural complications, and clinical and vascular imaging follow-up outcomes were retrospectively analyzed.

Results: Drug-coated balloon (DCB) dilatation of nonacute sICATO gives a 100% rate of successful recanalization, with a low complication rate (10.00%), good clinical outcomes (86.20%), low restenosis/reocclusion rate (3.45%), and one asymptomatic ipsilateral infarction (3.45%).

Conclusion: Drug-coated balloon dilation seems to be the promising treatment option for nonacute sICATO considering its safety and feasibility.

Keywords: drug-coated balloon, recanalization, nonacute symptomatic, intracranial carotid artery terminus, occlusion, endovascular treatment

INTRODUCTION

Intracranial atherosclerosis (ICAS) is an important cause of stroke leading to permanent damage to the brain, especially among Asian populations. Nonacute internal carotid artery occlusion (ICAO) may cause fluctuating clinical symptoms, namely, minor/major stroke or recurrent transient ischemic attack, or asymptomatic (1). The reason is that the blood supply reduction to the perfused territory is usually compensated by intracranial and extracranial–intracranial collaterals. Symptomatic cerebral ischemia associated with ipsilateral ICAO occlusion accounts for 5–8% of a recurrent ischemic stroke every year (2, 3). In addition, it is reported that among nonacute ICAO

patients with compromised hemodynamic status, recurrent stroke risk increases to ∼12% per year (4), even as high as 86% in a 7-year follow-up study (5).

Endovascular treatment is generally considered for nonacute ICAO if medical management, namely, dual-antiplatelet treatment (DAPT), statin, risk factor management, and lifestyle interventions fail or as a prophylaxis treatment for high-risk patients (6). Indication for endovascular treatment and the techniques used were not standardized. It is recommended among symptomatic patients with stage I or II hemodynamic failure (7).

A meta-analysis (8) reported endovascular treatment of nonacute ICAO limited to the cervical internal carotid artery (ICA) is feasible, with a 70% rate of successful recanalization. There were a few case-series studies that have reported stenting appeared to be safe and efficient for nonacute intracranial artery occlusion, including intracranial ICATO (9–11). Previous studies showed that the technical success rates of stenting for intracranial ICAO were high (10, 11). However, the reopened segment would be more prone to restenosis/reocclusion even after successful recanalization (9, 12, 13). The recanalization of the restenosis/reocclusion would be more difficult due to the stent.

Accordingly, there would need to be a viable alternative for nonacute ICAO recanalization. DCB, the coated balloon with antiproliferative drugs, paclitaxel, can effectively inhibit smooth muscle cells proliferation and migration by irreversibly stabilizing intracellular microtubules, therefore reducing the risk of restenosis compared with conventional balloon dilatation and stenting (14, 15). It is off-label used in the intracranial artery. Our previous experiences have shown the safety and feasibility of DCB for intracranial *de novo* atherosclerosis disease, with a lower incidence of restenosis (16, 17).

In this single-center study, we aimed to assess the feasibility and the safety of the endovascular treatment and to investigate if selected patients may benefit from DCB treatment when medical therapy failed in patients with nonacute sICATO underlying ICAS.

MATERIALS AND METHODS

Study Population

In this retrospective study, we recruited consecutive patients diagnosed with nonacute sICATO by digital subtraction angiography (DSA) in The First Affiliated Hospital of Shandong First Medical University between January 2016 and October 2020.

Intracranial atherosclerosis was the primary etiology for all target arteries. All patients had the instable clinical syndrome, such as recurrent transient ischemic attack (TIA), stroke, and neurologic deterioration (progressive or crescendo stroke). They did not achieve satisfactory improvement despite the best medical therapy (BMT), namely, DAPT, statin, blood pressure augmentation therapy, optimized glucose control, smoking cessation, and other lifestyle interventions. The occlusion length of type I lesions was <10 mm extending from the ophthalmic artery segment to the proximal anterior communicating artery. These lesions were detected by computed tomographic angiography (CTA), magnetic resonance angiography (MRA), and confirmed by DSA. Although DSA showed favorable patency of distal vasculature and collateral circulation, MRI depicted infarctions located at the cortical or subcortical borderzone territory and small infarction core shown on diffusion-weighted imaging (DWI) with a large area of low perfusion of ICA territory assessed by arterial spin labeling (ASL).

In this study, other potential causes of occlusion, such as vasculitis, Moyamoya syndrome, emboligenic heart, or arterial dissection were not included. Patients who had no recurrent ischemic events after BMT were not included. If the collateral circulation between the anterior cerebral artery and/or posterior cerebral artery was well-developed and perfusion of ICA territory assessed by DSA was adequate, patients did not need the procedure.

All the enrolled patients or their authorized surrogates knew the risks and benefits of endovascular treatment, including the off-label use of the coronary DCB and gave a written informed consent in accordance with the Declaration of Helsinki. The institutional review board of The First Affiliated Hospital of Shandong First Medical University approved the study without registration owing to its retrospective nature.

Preprocedural Medical Management

A DAPT with 100 mg aspirin and 75 mg clopidogrel was routinely maintained for at least 5 days before the procedure. Thromboelastography platelet mapping was tested to assess bleeding risk and guide perioperative DAPT. If drug inhibition occurs, the effectiveness of the drug can be guaranteed by increasing the dosage or changing the drug, such as ticagrelor. If the bleeding risk elevates, decreasing the drug dosage can adjust the effectiveness. All patients were given individual standard medical treatment and lifestyle interventions, namely, antihypertensive agents, antidiabetic drugs, and statins.

Intervention Procedure

All the procedures were performed *via* the percutaneous transfemoral route under general anesthetic. Heparin was administered intravenously to keep the activated clotting time between 250 and 300 s during the procedure.

A 6F 90-cm-long sheath and Catalyst 058 115 cm intermediate catheter coaxially advanced until catalyst reached the proximal to the ophthalmic artery. A 0.014 Synchro microguide wire (Stryker Neurovascular, Salt Lake City, Utah, USA) was used to enter the occluded internal carotid terminus with the support of an Excelsior SL-10 soft microcatheter (Stryker Neurovascular, Cork, Ireland). Once we cross the proximal occlusion, the microcatheter was advanced until we reach the patent lumen. Through the microcatheter angiography, the length of the occlusion and distal lumen of the lesion were confirmed after withdrawing the microguidewire. Once it is confirmed, the microguide wire was advanced through the microcatheter and positioned in the M2 segment. We then use the microguide wire as a railroad for delivering different devices to reconstruct the occluded segment from distal to proximal. The lesions were initially inflated with conventional balloons (Gateway

balloon, Boston Scientific, Maple Grove, Minnesota, USA). The subsequent application of paclitaxel-coated coronary balloon (SeQuent Please, B. Braun, Berlin, Germany) and/or stent depended on the decision of the operator. The application method of the DCB was the same as described in our previous study (16). The intervention was considered a technical success if the occlusion segment was processed with establishing grade 2b-3 antegrade thrombolysis in cerebral ischemia (TICI) flow. Residual stenosis is defined as > 50% stenosis at the end of the intervention.

Postprocedural Management

After the procedure, a cerebral CT scan was performed immediately. And all patients were intensively monitored including keeping the systolic blood pressure ≤ 130 mmHg and documenting neurological symptoms/signs. Assessment of the National Institutes of Health Stroke Scale (NIHSS) score was performed by the neurologist within 24 h after the procedure. The investigated complications included distal embolization, intracranial hemorrhage, hyperperfusion syndrome, dissection, and death.

Follow-Up Management and Data Collection

Aspirin 100 mg with clopidogrel 75 mg/day or ticagrelor 90 mg two times 1 day was maintained for 3 months for patients with only DCB dilatation, 6 months for patients with remedial stenting implantation. Then the dual antiplatelet regimen was transitioned to a single antiplatelet (aspirin or clopidogrel or ticagrelor) therapy to be continued for the lifetime of patients.

We collected the demographic, clinical, angiographic, and procedural data. All patients underwent clinical follow-up at 1 month, 3 months, 6 months, and 1 year to evaluate the functional outcome and rates of recurrent TIA, stroke, and death. The NIHSS and the modified Rankin Scale (mRS) were used to, respectively, access the severity of the clinical stroke and functional outcome at admission, preprocedure, 24 h postprocedure, at discharge, 30-day postprocedure, and every follow-up. The mRS is commonly applied to assess the degree of disability in patients suffering a neurological event, ranging from 0 (asymptomatic) to 6 (death) in our study (18). A favorable functional outcome was defined as the mRS score ≤2 at 3 months.

All the patients were scheduled to reperform vascular imaging examination at 3 months for patients with only DCB dilatation, 6 months for patients with remedial stent implantation. DSA was preferred, but MRA/CTA was also accepted for some patients who refuse to perform DSA. Angiographic or in-stent restenosis (ISR) was defined as, within or immediately adjacent (within 5 mm) of the treated segment, a diameter of the stenosis >50% for Preoperative residual stenosis ≤30 or >20% absolute luminal loss for Preoperative residual stenosis >30%. Angiographic or in-stent reocclusion was defined as the recanalized lumen being completely lost. Consensus resolved disagreements. The restenosis/reocclusion, associated with ischemic symptoms of the offending vessel territory, is called symptomatic restenosis/reocclusion.

TABLE 1 | Baseline demographic and clinical characteristics of patients.

Characteristics	*n* = 30
Demographics	
Sex, male	16 (53.33%)
Female	14 (46.67%)
Age, years, mean ± SD	57.27 ± 10.12
Medical history	
Hypertension	20 (66.67%)
Diabetes mellitus	13 (43.33%)
Hyperhomocysteine	10 (33.33%)
Cardiovascular disease	6 (20.00%)
Hyperlipidaemia	5 (16.67%)
Atrial fifibrillation	2 (6.67%)
Smoking	12 (40.00%)
Clinical	
mRS, median (IQR)	2.0 (1–4)
NIHSS, median (IQR)	3.0 (0–7.5)
Preoperative NIHSS, median (IQR)	3.0 (0–9.25)

mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range.

Statistical Analysis

Descriptive statistics were used in this study. Continuous data were expressed as the mean ± SD or as the median with interquartile range (IQR). It was compared by using the Student's *t*-test or the Mann–Whitney *U*-test. Categorical data were expressed as numbers and percentages, and compared using the chi-squared or Fisher's exact test. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of Patients

A total of 30 patients, 16 males and 14 females (53.33%, 46.67%), were enrolled in this study. The baseline demographic and clinical characteristics of the 30 patients are given in **Table 1**. The mean age of the enrolled patients was 57.27 ± 10.12 years, with no gender differences. The primary medical history of these patients included hypertension (20, 66.67%), diabetes mellitus (13, 43.33%), hyperhomocysteine (10, 33.33%), cardiovascular disease (6, 20.00%), hyperlipidemia (5, 16.67%), and atrial fibrillation (2, 6.67%). Hypertension ($N = 20$, 66.67%), diabetes mellitus ($N = 13$, 43.33%), and smoking (12, 40.00%) were the most common risk factors. The median NIHSS and the mRS scores at baseline were 3.0 (0–7.5) and 2.0 (IQR, 1–4), respectively.

Preoperative MRI and Angiographic Findings

Magnetic resonance imaging results revealed acute infarcts in the cerebral hemisphere (involving the frontal lobe, temporal lobe, parietal lobe, occipital lobe, semiovale center, basal ganglia area, and corona radiata area), usually presenting as a watershed infarction (**Figure 1A**). ASL assessed complete

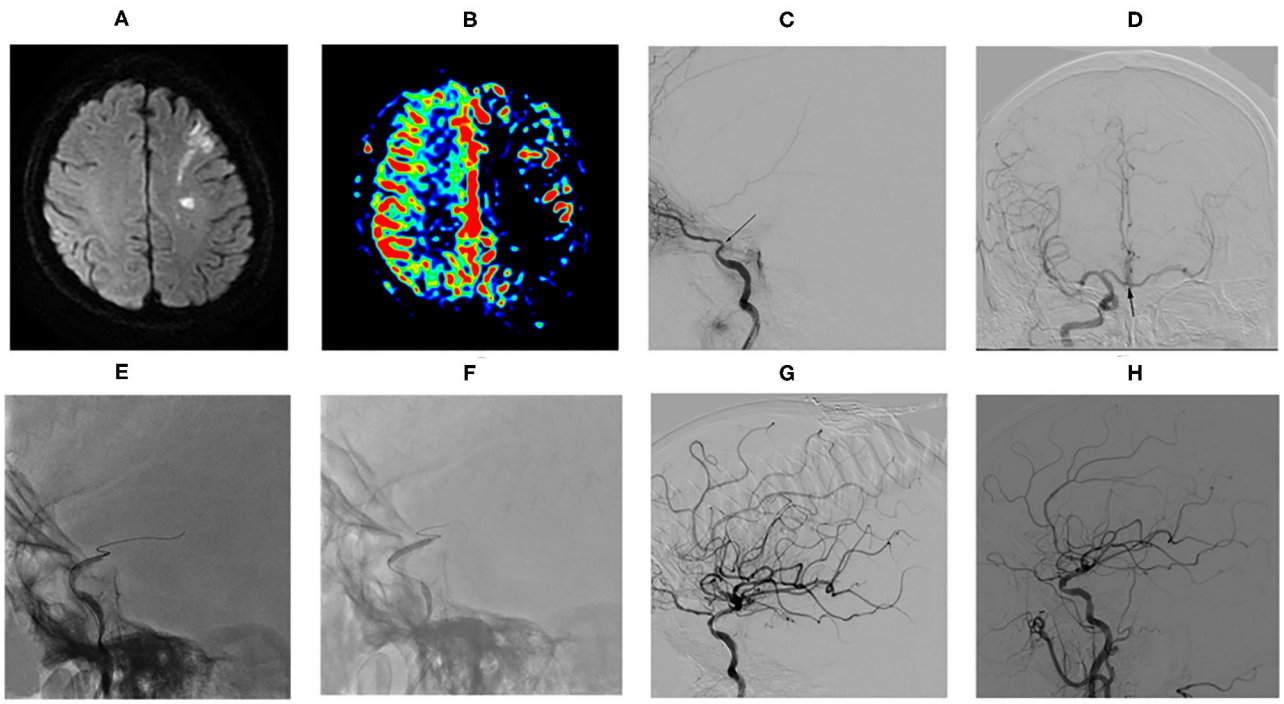

FIGURE 1 | Example of drug-coated balloon (DCB) dilatation for nonacute sICATO and follow-up. **(A)** MRI revealed left watershed infarction. **(B)** ASL showed left cerebral hemispheric hypoperfusion in the ICAO territory. **(C)** DSA confirmed the left internal carotid artery terminus occlusion ipilaterally to the infarcts (arrow). **(D)** DSA showed anterior communicating arteries (arrow). **(E)** Predilatation with a conventional balloon. **(F)** DCB dilatation after predilatation. **(G)** Angiographic result after the procedure. **(H)** Angiographic result at follow-up of 3.0 months.

or partial hypoperfusion in the ICAO territory (**Figure 1B**). CTA/MRA detected the internal carotid artery terminus occlusion (ophthalmic segment, C6 and/or communicating segment, C7) ipsilaterally to the infarcts. The above were confirmed by DSA (**Figure 1C**). In addition, DSA showed all patients had collateral circulation, at least including one of the primary collaterals (anterior and/or posterior communicating arteries, AcomA and/or PcomA) (**Figure 1D**) and the secondary collaterals (leptomeningeal and/or ophthalmic arteries LC and/or OAs).

Procedural Characteristics

Overall, the median time from the symptom onset to treatment and the occlusion confirmed to treatment was 29 days (range, 6.0–270.0 days; IQR, 20.0–67.5 days) and 26 days (range, 7.0–300.0 days; IQR, 18.0–75.0 days), respectively. All patients achieved stable antegrade perfusion with TICI 3 in 16 cases (16/30, 53.33%) and TICI 2b in 14 cases (14/30, 46.67%). Among the 30 successful patients, DCB angioplasty (**Figures 1E–H**) was only applied in 22 patients, while DCB angioplasty plus remedial stenting was applied in 8 patients. The postprocedure stenosis was 14.0 ± 21.1%. The residual stenosis rate was 6.67% (2/30). A total of 4 cases had no residual stenosis but the lumen wall was irregular because of neointima formation, vascular remodeling, or plaque. Asymptomatic vessel dissection after DCB inflation occurred in 1 patient (3.33%). No obvious periprocedural complications and hemorrhage happened. Remedial stenting was not performed due to table antegrade perfusion with TICI 2b in this patient. Periprocedural distal embolization strokes occurred in 2 patients (6.67%). They had blurred vision on the ipsilateral to the recanalized vascular. Other common periprocedural complications, such as cerebral hemorrhage, hyperperfusion syndrome, or death did not occur in this case series. The treatment modalities and outcomes of the 30 patients are summarized in **Table 2**.

Clinical and Angiographic Outcomes

One patient was lost during the follow-up. The rest of 29 patients (96.67%) all received clinical follow-up with no death, and 21 of them (70.00%) were followed up radiologically. During the clinical follow-up period of 7.02 ± 3.65 months, a new asymptomatic ipsilateral infarction based on MRI occurred in 1 patient at 30 days (3.45%). After 3 months, this patient herself transited a dual antiplatelet regimen to a single antiplatelet (aspirin) therapy without any further vascular imaging examination. The patient who had symptomatic vessel dissection experienced the asymptomatic reocclusion of the recanalized R-ICA terminus at 30-day angiographic follow-up. After 4 months, this patient developed paroxysmal dizziness and numbness in the left limb with DWI detecting no new ischemic lesion.

TABLE 2 | Angiographic and procedural characteristics.

Characteristics	*n* = 30
Timing	
Symptom onset to treatment, days, median (IQR)	29 (20.0–67.5)
Occlusion confirmed to treatment, days, median (IQR)	26 (18.0–75.0)
Technical success[a]	30 (100%)
Modality of recanalization	
Angioplasty with DCB	22 (73.33%)
Angioplasty with DCB and remedial stenting	8 (26.67%)
Postprocedural Perfusion	
TICI = 2b	14 (46.67%)
TICI = 3	16 (53.33%)
Residual stenosis[b]	2 (6.67%)
Complication rate	
Distal embolization	2 (6.67%)
Dissection	1 (3.33%)
Hyperperfusion syndrome	0
ICH	0
Death	0

[a] *Technical success, defined as TICI ≥ 2b at the end of the intervention.*
[b] *Residual stenosis, defined as > 50% stenosis at the end of the intervention.*
DCB, drug-coated balloon; TICI, thrombolysis in cerebral ischemia; ICH, intracranial hemorrhage.

The proportion of patients with a good clinical outcome (mRS score 0–2) was 86.20% (25/29), and 89.66% (26/29) achieved an acceptable outcome (mRS score 0–3). A total of 3 patients received mRS score of 4 at the final clinical follow-up. There was a significant difference between the follow-up mRS and the Preoperative mRS ($p = 0.00$, <0.05). During the vessel imaging examination at 8.02 ± 3.65 months, cerebral angiography was obtained for 23 patients (76.67%). DSA follow-up and MRA/CTA follow-up were available for 16 patients and 7 patients, respectively. No restenosis/ISR occurred. There was no significant difference between the follow-up and the postoperative residual stenosis ($p = 0.072$, >0.05). Residual stenosis degree in 2 cases was reduced to ≦50% at follow-up. As shown in **Figure 2**, this patient who was found a large number of thrombus during the occlusion recanalization with 70% residual stenosis, reexamined DSA showing thrombus disappeared and residual stenosis rate improved with 50% residual stenosis at 30-day angiographic follow-up. Another patient was found residual stenosis rate reducing from 60 to 40%. There was no significant difference between the follow-up and the postoperative TICI grade ($p = 0.136$, >0.05). But among 9 patients who achieved postprocedural stable antegrade perfusion with TICI 2b, 7 patients received the significantly improved TICI grade from 2b to 3 (77.78%) at angiographic follow-up.

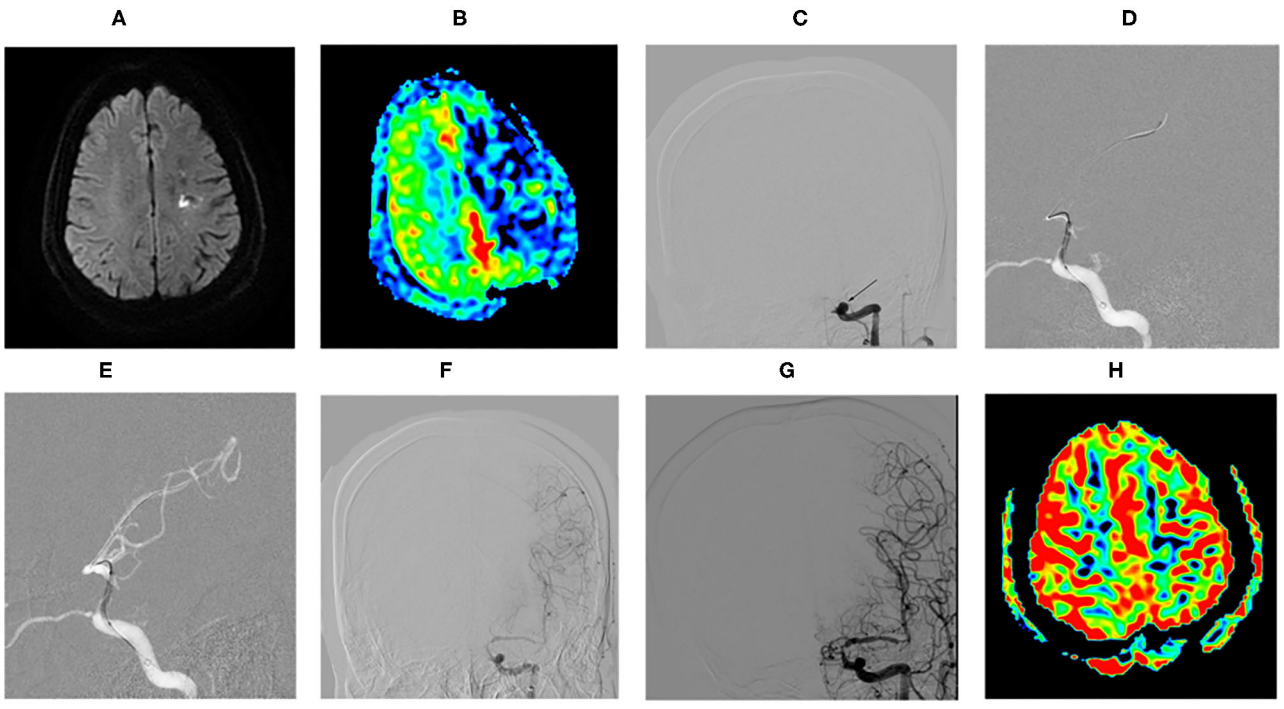

FIGURE 2 | Example of comparing the preoperative MRI and operative angiographic findings with follow-up. **(A)** MRI revealed left watershed infarction. **(B)** ASL showed left cerebral hemispheric hypoperfusion in the ICAO territory. **(C)** DSA confirmed the left internal carotid artery terminus occlusion ipilaterally to the infarcts (arrow). **(D)** Predilatation with a conventional balloon. **(E)** DCB dilatation after predilatation. **(F)** DSA showed the occlusion recanalization with 70% residual stenosis with a large number of thrombus (arrow). **(G)** DSA showed thrombus disappeared and residual stenosis rate improved with 50% residual stenosis at angiographic follow-up of 1 month (arrow). **(H)** ASL showed basically symmetric bilateral cerebral hemispheric perfusion at angiographic follow-up of 1 month.

DISCUSSION

In this single-center retrospective pilot study, we found that DCB angioplasty was feasible and safe in the treatment of patients with nonacute sICATO.

Nonacute progression of occlusive lesions may permit distal collateral development to avert major ischemic events. The primary collaterals include ACoM or PCoM and secondary, LC or OA. The availability of collateral supply tends to curb the potential ischemic injury. The patients suffering from nonacute ICAO are usually asymptomatic or cause fluctuating clinical symptoms, including recurrent transient ischemic attack or minor/major stroke (1). Until collateral circulation cannot compensate for the reduced downstream perfusion or emboli fall from the stump of the ICA *via* collaterals (19–21), ischemic stroke symptoms appear with radiography depicting infarcts in the cortical or subcortical borderzone territory (anterior borderzone between ACA and MCA territories and posterior borderzone between MCA and PCA territories) ipsilateral to the occlusion. The internal carotid artery terminus is located between the ophthalmic artery segment and the proximal anterior communicating artery with the opening of the PcomA or AcomA. It is a relatively short occlusion ($\leq$10 mm). The location of the vascular occlusion is important because of the good reconstruction of distal collateral vessels from the PcomA or AcomA, in that ICA occlusions were significantly correlated with both mortality and good clinical outcome. Our patients having recurrent cerebral ischemic symptoms despite BMT with favorable collateral circulation shown by DSA were chosen to recanalize the occlusive ICA. Our results suggest that patients with an occlusion of the ICA terminus had a high rate of successful recanalization, low periprocedural major complications, and better follow-up patency rates. This finding is consistent with previous research (22).

The incidence of ISR increases the risk of recurrent ischemic events. Symptomatic ISR was ∼9.6–14.0% (23–25). A high ISR rate is a challenge for intracranial stenting. DCB could effectively reduce the risk of restenosis/reocclusion. Patients are allowed to receive noninvasive magnetic resonance examination because of no mechanical scaffold after DCB angioplasty, which reduces the technical difficulty of treating re-events. SeQuent Please DCB was initially designed for coronary arteries. For intracranial arteries, the DCB might be not a suitable size and its tip might be somewhat rigid. Meanwhile, an excessively tortuous vessel pathway increases the difficulty and risk of the procedure. Therefore, we strictly evaluated the vessel path to select the proper patient. During the procedure, an intracranial support catheter helps navigate to the target artery, which might have accounted for the higher arrival rate of DCBs compared with a previous report (26). In addition, for the drug working on the blood vessel walls better, it is important to use a bare balloon for the lesion predilation before DCB inflation.

In this study, only 2 patients (2/30, 6.67%) had blurred vision on ipsilateral to the recanalized vascular owing to the distal embolization. It is similar to our initial experience (16) and some small sample studies (27, 28). Re-events occurred rate is obviously low about 3.35% (1/29) in this study, which is according to our initial experience (16) and further research (17). The patient who had dissection with stable antegrade perfusion after the operation did not perform stent. This patient experienced the reocclusion of the recanalized R-ICA terminus at a 30-day angiographic follow-up. Therefore, further study will investigate the timing of remedial stenting and compare the re-events occurred rate between DCB dilation with and without a remedial stent.

Although there was no statistically significant difference in either residual stenosis or TICI grade, the residual stenosis, and irregular vascular walls, were improved, even became regular vascular walls at angiographic follow-up. Therefore, our study showed that the role of DCB seems to be just as important in vascular remodeling and patency improvement for intracranial arteries as for coronary artery disease (25).

In this study, all the 30 arteries achieved good lumen patency and antegrade flow. A total of 8 patients underwent remedial stent implantation, usually self-expanding stent or balloon-mounted stent, due to unsustainable effective antegrade flow, and 22 patients recanalized with DCB only. Except for 1 patient lost during follow-up, 26 of the rest 29 patients achieved acceptable clinical follow-up outcomes. Compared with preprocedure, most patients showed statistically significant improvement at mRS score at follow-up. The reason for mRS grade 4 seems to be massive cerebral infarction (1/30) or progressive stroke (2/30) leading to severe neurological impairment. Even the occlusive artery recanalized and postoperative rehabilitation exercise continued, but it did not work.

Limitations

There are several limitations in this study. First, the mean age of the patients was 57 years, a little younger than the average patients with ICAS, there might be a selection bias. It might be because this study is of a retrospective nature and monocentric design with not large enough sample size. In the future, randomized controlled trials are needed to eliminate the age bias and investigate whether this treatment compares favorably with BMT and non-DCB therapy in these patients. Second, MRA and CTA follow-up were performed in some patients so that detail may partly jeopardize the consistency. Third, the angiographic follow-up time was scheduled for <1 year, the efficacy of the procedure needs to be re-evaluated during a long-term follow-up. Therefore, we need to develop a more reasonable follow-up plan and strengthen follow-up management.

Interpretation

To the best of our knowledge, this is the first case series of patients with nonacute sICATO treated with DCB. We systematically reviewed the safety and efficacy of DCB. DCB-oriented angioplasty might be considered a viable alternative treatment for patients with nonacute sICATO who failed standard medical treatment.

CONCLUSION

This series study shows that DCB may be feasible and safe for nonacute atherosclerotic sICATO disease with recurrent stroke attributed to impaired cerebral hemodynamics refractory to medication in carefully selected patients. It should be emphasized that revascularization of nonacute sICATO is a high-risk procedure; therefore, the selection of eligible patients and perfect treatment of complications are equally critical. Further prospective randomized studies with larger patient numbers and longer follow-up periods are mandatory to investigate the clinical efficacy and indications of the procedure.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Shandong First Medical University. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JH, HY, and JiZ: study concepts and design. HY and MZ: statistical analysis. HY, JiZ, JuZ, YS, and LS: manuscript composition. HY, WZ, and JH: manuscript revision. All authors contributed to the article and approved the submitted version.

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frontiers in Neurology

CASE REPORT
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Case Report: Sequential Transarterial and Trans-Cortical Venous Embolization of a Mixed Pial-Dural AVM

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Endovascular therapy is the primary treatment modality for dural arteriovenous fistulas. Pre-treatment angiographic evaluation of dural fistulas must rule out the presence of a mixed pial component or supply from pial-dural collaterals, as the pial supply must be closed before definitive occlusion of the draining vein to prevent iatrogenic rupture. In this report, we described a case of a mixed pial-dural arterial venous malformation (AVM), which was effectively treated with a sequential transarterial and trans-cortical venous embolization.

Keywords: pial-dural AVM, transarterial embolization, transvenous embolization, dural AV fistula, facial arcade

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INTRODUCTION

Endovascular therapy is the primary treatment modality for dural arteriovenous fistulas (dAVFs). The presence of a mixed pial component or supply from pial-dural collaterals is rare, however should be identified prior to treatment. In this report, we described a case of a mixed pial-dural arterial venous malformation (AVM), which was effectively treated with a sequential transarterial and trans-cortical venous embolization.

CASE PRESENTATION

We reported the case of a 73-year-old female with coronary artery disease, hypertension, and hyperlipidemia who underwent embolization of a symptomatic mixed pial-dural AVM. She presented with left-sided paresthesias, and MRI demonstrated a bilobed flow void in the right cerebral peduncle contiguous with a pial vein and with surrounding edema and/or gliosis (**Figure 1**). Cerebral catheter angiography revealed a Cognard type IV/Borden type III mixed pial-dural fistula along with the tentorial attachment to the right petrous apex. Arterial supply to a small nidus was from 2 branches of the right superior cerebellar artery (SCA) and the petrosal branch of the right middle meningeal artery (MMA) (**Figures 2A,B**). Venous drainage was into an isolated segment of the superior petrosal sinus which drained *via* a bridging vein into the anterior pontomesencephalic system. This in turn drained into the right basal vein of Rosenthal *via* the peduncular vein. At the junction of the anterior mesencephalic and peduncular veins was a posteriorly directed bilobed venous varix which measured 13 mm in length × 5 mm in width (**Figures 2C,D**). Eight weeks after clinical presentation, she underwent elective transarterial and transvenous embolization of the pial-dural AVM.

Procedure

The procedure was performed under general anesthesia. Through a left radial artery approach, a Benchmark catheter was placed into the V3 segment of the left vertebral artery. Venous access was obtained transfemorally.

To minimize the risk of AVM rupture, transarterial closure of the pial supply from the right SCA was performed prior to transvenous occlusion of the recipient venous pouch. To ensure transvenous access for treatment, a microcatheter was placed into the venous pouch prior to transarterial embolization. A Ballast 80 cm 8F catheter (Balt, Irving, CA) was placed at the right jugular bulb. Through the Ballast, a Sofia Flow Plus 6F catheter (MicroVention, Aliso Viejo, CA) intermediate catheter was advanced over a Headway Duo 156-cm microcatheter and Synchro Select microwire into the right vein of Galen. To reach the recipient vein, the microcatheter was replaced with a Headway Duo 167 cm (MicroVention, Aliso Viejo, CA) microcatheter. Over a Traxcess microwire (MicroVention, Aliso Viejo, CA), this microcatheter was carefully advanced past the varix, through the anterior pontomesencephalic system, and into the venous pouch using a roadmap from the left vertebral artery injection (**Figures 3A,B**).

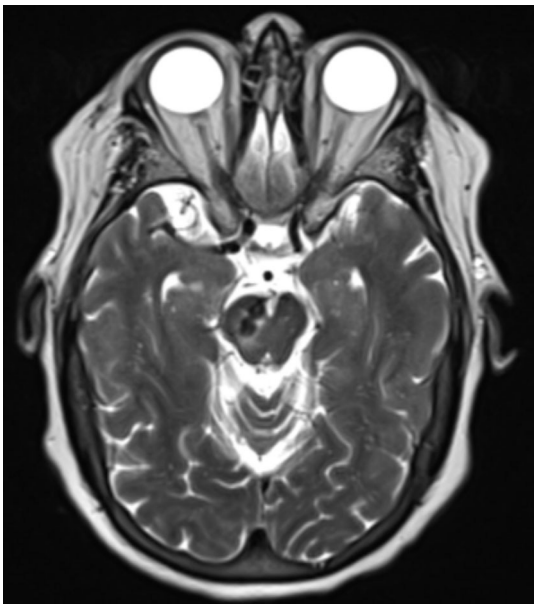

FIGURE 1 | Axial T2 weighted image demonstrates bilobed flow void within the right cerebellar peduncle with surrounding edema and/or gliosis.

Then, through the Behnchmark catheter (Penumbra, Alameda, CA), a Sofia 5F catheter (MicroVention, Aliso Viejo, CA) was navigated into the basilar artery over a Headway Duo 156 cm, 167 cm (MicroVention, Aliso Viejo, CA) microcatheter and Synchro select microwire (MicroVention, Aliso Viejo, CA). The microcatheter was placed into the right SCA and advanced into one of the branches supplying the AVM nidus. The microcatheter was placed just proximal to the takeoff of a tiny pedicle supplying the lateral aspect of the nidus. Given the small caliber of the pedicle, it was decided to close the branch from this position with additional non-target embolization of supply to the superior and lateral aspect of the right cerebellum. A small amount of Onyx 18 (Medtronic, Minneapolis, MN) (<0.2 ml) was injected to achieve proximal closure of the small feeding pedicle, and the microcatheter was retrieved. Through the 5F SOFIA, another Headway Duo 156-cm microcatheter was advanced into a direct feeder supplying the medial aspect of the AVM nidus. A small amount of Onyx 18 (<0.2 ml) was injected achieving closure of the pedicle with partial penetration of the nidus. The microcatheter was retrieved.

After the closure of the pial supply to the AVM, a second Benchmark catheter was placed into the right common carotid artery where angiography confirmed arterial supply to the dural

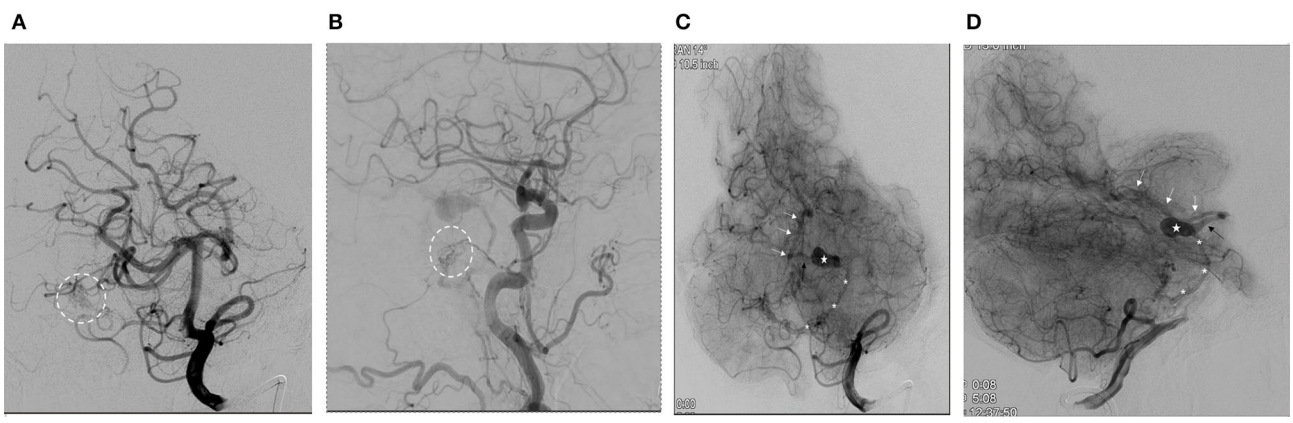

FIGURE 2 | (A) Anterior-posterior oblique projection (arterial phase) demonstrates right superior cerebellar artery (SCA) supply to the arterial-venous malformation (AVM) nidus (dashed circle). **(B)** Lateral projection from right common carotid artery injection (arterial phase) demonstrates supply to the dural fistulous network (dashed circle) from the petrosal branch of the middle meningeal artery. **(C)** Anterior-posterior oblique projection from left vertebral artery injection (parenchymal phase) demonstrates the venous drainage from the AVM. (*, anterior pontomesencephalic vein; star, venous varix; black arrow, peduncular vein; white arrows, a basal vein of Rosenthal). **(D)** Lateral projection from left vertebral artery injection (parenchymal phase) demonstrates the venous drainage from the AVM. (*, anterior pontomesencephalic vein; star, venous varix; black arrow, peduncular vein; white arrows, a basal vein of Rosenthal).

component of the AVM *via* the petrosal branch of the right MMA. To facilitate controlled Onyx embolization of the venous pouch, two Target 360 Nano coils (3 mm × 4 cm, 2 mm × 3 cm) were placed into the pouch through the Headway 167-cm microcatheter.

After the closure of the pial supply to the AVM, a second Benchmark catheter was placed into the right common carotid artery where angiography confirmed arterial supply to the dural component of the AVM *via* the petrosal branch of the right MMA. To facilitate controlled Onyx embolization of the venous pouch, two Target 360 Nano coils (3 mm × 4 cm, 2 mm × 3 cm) were placed into the pouch through the Headway 167-cm microcatheter. Then, ∼0.3 ml Onyx 18 was injected until the recipient vein was occluded (**Figure 3C**). Progress was monitored with intermittent injections of the right CCA. After the closure of the AVM, the venous microcatheter was retrieved.

Patient Outcomes

Postoperatively, the patient was monitored in the Neuro ICU. She reported mild nausea, unsteady gait, and right-handed clumsiness. Follow-up MRI showed an expected infarct in the right superior and lateral cerebellar hemisphere and thrombosis of the venous varix (**Figures 4A–C**). She was discharged on day 7 after admission to inpatient rehab. At 3 months, she was living alone at home. She had residual mild balance difficulty but could ambulate independently with a walker. Her mRS score was 2.

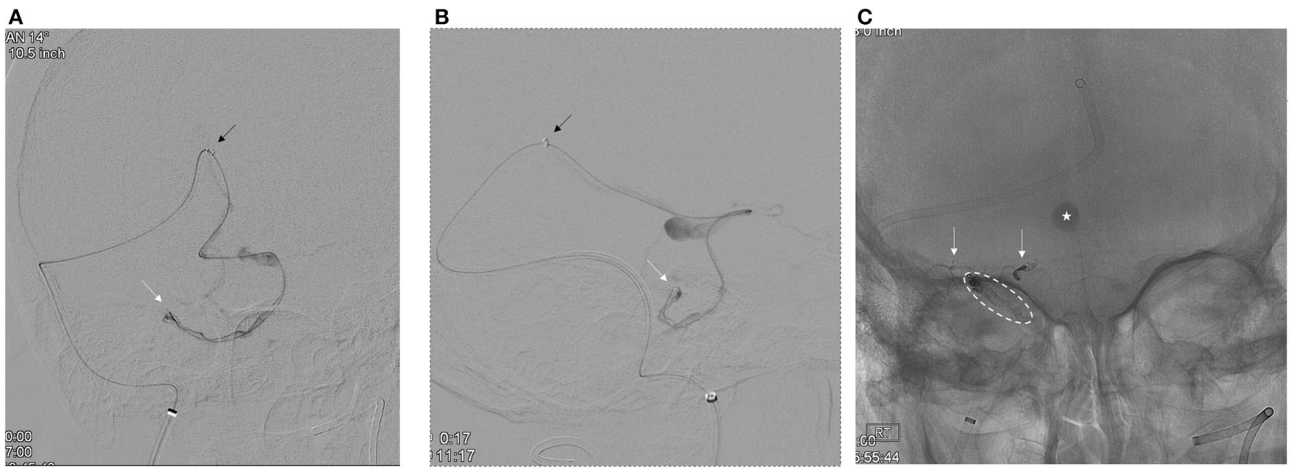

FIGURE 3 | (A,B) Superselective microcatheter angiogram [**(A)**, AP oblique; **(B)**, lateral] confirms the microcatheter tip position (white arrow) within the recipient venous pouch. The intermediate catheter (black arrow) is in the distal vein of Galen. **(C)** White arrows delineate the Onyx casts within the arterial pedicles from the right SCA. Dashed oval circumscribes the coil and Onyx cast within the recipient venous pouch and the bridging vein. The star illustrates contrast stasis within the venous varix.

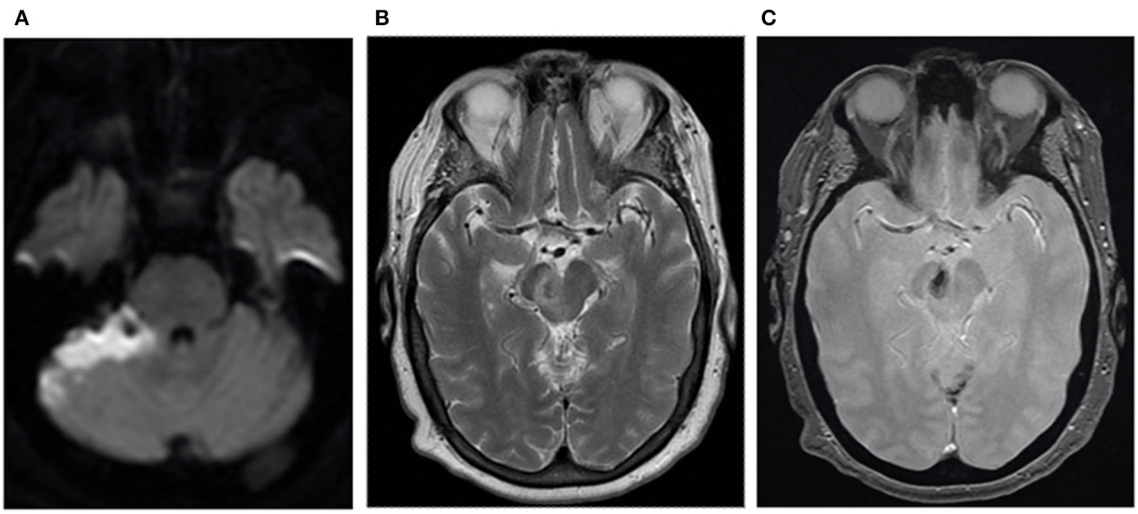

FIGURE 4 | (A) Axial DWI image reveals acute infarct within the superior and lateral aspect of the right cerebellum. **(B)** Axial T2 weighted image reveals loss of the flow void within the venous varix in the right cerebral peduncle with surrounding edema. **(C)** Axial GRE image reveals thrombus within the venous varix.

DISCUSSION

Angiographic evaluation of dAVFs must rule out the presence of a mixed pial component or supply from pial-dural collaterals (e.g., the artery of Davidoff and Schechter), as endovascular treatment must occlude the pial supply prior to closure of the dural fistula. Because definitive treatment of dural fistulas requires closure of the recipient vein, the presence of a mixed pial component or pial collateral supply can result in AVM rupture due to outflow obstruction as seen with brain AVMs (1, 2).

Owing to the dural supply from the petrosal branch in this case, transvenous embolization was necessary to prevent injury to the facial arcade. The ability to traverse the cortical veins of the posterior fossa to reach the venous pouch illustrates the increased safety profile afforded by the current generation of highly compliant and deliverable intermediate catheters and microcatheters. Endovascular closure of the draining vein can be achieved using coils, liquid embolic agent, or a combination as in this case. Flow-directed microcatheters that can also deliver detachable coils are particularly useful for this application. Depending on the length and tortuosity of the cortical venous drainage, it is often not possible to achieve transvenous access to the fistula site, in which case a multimodal approach using radiosurgery or neurosurgery is necessary.

A unique feature of this case was the relative prominence of the venous varix which was disproportionate to the overall degree of venous ectasia. The size of the varix and its eloquent location with the cerebral peduncle contributed to the patient's neurological deficit in the absence of rupture.

CONCLUSION

Endovascular therapy is the mainstay of treatment for dAVFs. Mixed pial-dural AVMs are rare lesions that are important to identify because treatment must target the pial supply prior to definitive closure of the draining vein to prevent iatrogenic rupture.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author(s).

ETHICS STATEMENT

Ethical review and approval was not required for the current study in accordance with the local legislation and institutional requirements. Written informed consent was not required for the current study in accordance with the local legislation and institutional requirements. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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CASE REPORT
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Case Report: "Clipping" an Internal Carotid Artery Aneurysm With a Duplicated Middle Cerebral Artery and the Anterior Choroidal Artery Arising From the Dome

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Background: A duplicated middle cerebral artery (DMCA) is an anatomical variant that includes duplication of the middle cerebral artery (MCA) and an anomalous vessel originating between the anterior choroidal artery (AChA) and the distal end of the internal carotid artery (ICA). Here, we present a case report of an ICA aneurysm with a DMCA and the AChA originating from the dome, which was successfully treated with clipping.

Case Description: In a 64-year-old man, preoperative angiography revealed an unruptured right ICA aneurysm with a maximum diameter of 4.3 mm, and fusion three-dimensional computer graphics revealed that a DMCA and the AChA originated from the dome. The aneurysm enlarged; therefore, clipping was performed. The closure of the aneurysm while preserving the patency of the DMCA and AChA was identified using intraoperative microvascular Doppler ultrasonography and indocyanine green video angiography. The postoperative course was uneventful, and no ischemic lesions were confirmed on MR imaging.

Conclusion: To the best of our knowledge, this is the first report of an ICA aneurysm with a DMCA and the AChA arising from the dome. In such cases, the anatomy of the DMCA and AChA should be well-characterized before treatment.

Keywords: duplicated middle cerebral artery, cerebral aneurysm, anterior choroidal artery, branch incorporated aneurysm, clipping, fusion three-dimensional computer graphics

INTRODUCTION

A duplicated middle cerebral artery (DMCA) is a normal variation of the middle cerebral artery (MCA), in which the MCA originates between the anterior choroidal artery (AChA) and the distal end of the internal carotid artery (ICA), and this passes into the sylvian fissure and perfuses part of the territory of the MCA (1, 2). The treatment of aneurysms at the origin of the DMCA has been reported previously (3–5). When treating aneurysms arising from the origin of the DMCA, it is important to preserve the AChA which branches nearby. We present a case in which clipping was performed for an ICA aneurysm with a DMCA and the AChA arising from the dome. There are no

reports of aneurysms in which both a DMCA and the AChA branch from the dome. This report discusses the anatomical aspects of these aneurysms.

CASE DESCRIPTION

A 64-year-old man was referred to our hospital because of an unruptured right ICA aneurysm that was detected incidentally on time-of-flight MR angiography (**Figures 1A,B**). Cerebral digital substruction angiography revealed an unruptured aneurysm with a maximum diameter of 4.3 mm at the supraclinoid portion of the right ICA (**Figure 1C**), and three-dimensional rotational angiography demonstrated that a DMCA and the AChA originated from the dome (**Figure 1D**). Additionally, fusion three-dimensional computer graphics integrating MR imaging and digital substruction angiography revealed that the DMCA passed through the sylvian fissure along the M1 segment of the MCA (**Figure 1E**) and perfused the anterior temporal lobe (**Figure 1F**). The fusion three-dimensional computer graphics was reconstructed using GRID 1.1 (Kompath Inc., Tokyo, Japan), utilizing the multi-threshold technique, as described previously (6–8). In summary, preoperative images were the output from the DICOM (digital imaging communication in medicine) format; they were imported into the image processing software GRID, which implements automatic registration of multiple imaging modalities. The multi-threshold is a method for extracting both thick and thin blood vessels with different threshold values. Microvessels can be visualized with less noise using this method (7). The patient had a family history of subarachnoid hemorrhage. The aneurysm increased to 4.3 mm after 10 years of follow up; it was 3 mm at the time of detection. Therefore, we determined that an intervention was required. The risk of occlusion of the arteries branching from the dome was estimated to be high if endovascular treatment was performed. In order to preserve the incorporated branch arteries, we decided to perform clipping. A right frontotemporal craniotomy was performed using a transsylvian approach to the aneurysm. Intraoperative findings showed that the DMCA and the AChA branched from the dome of the ICA aneurysm (**Figure 2A**). Two titanium clips were combined and applied to occlude most part of the aneurysm, while confirming the patency of the DMCA and the AChA (**Figure 2B**). Aneurysm obliteration and the patency of the parent and branch vessels were confirmed using intraoperative microvascular Doppler ultrasonography and indocyanine green video angiography (**Figure 2C**). Postoperatively, there were no neurological deficits or ischemic lesions on MR imaging.

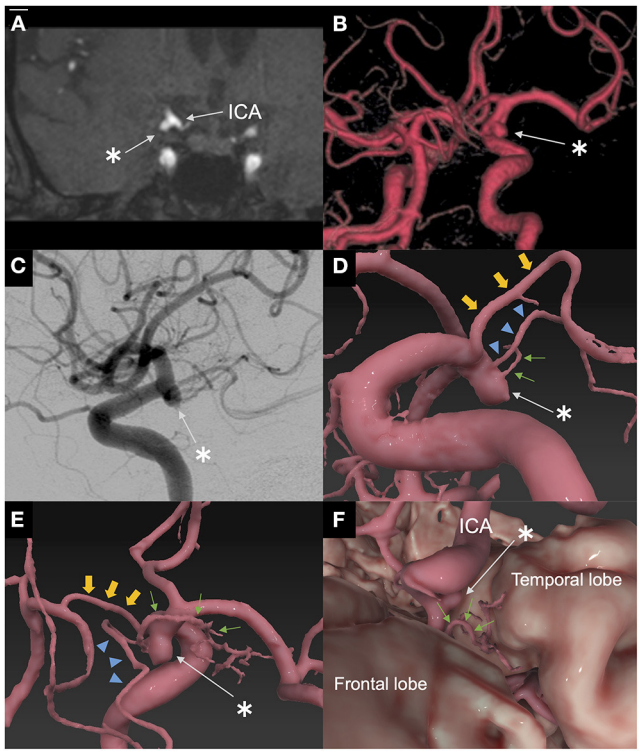

FIGURE 1 | Preoperative imaging. **(A)** Coronal plane of time-of-flight magnetic resonance angiography on admission. Coronal plane of time-of-flight magnetic resonance angiography showed an unruptured aneurysm of the right internal carotid artery in contact with the temporal lobe. *: aneurysm. **(B)** Three-dimensional time-of-flight magnetic resonance angiography on admission. Three-dimensional time-of-flight magnetic resonance angiography showed an unruptured aneurysm of the right internal carotid artery supraclinoid portion. *: aneurysm. **(C)** Lateral view of digital subtraction angiography of the right internal carotid artery. Lateral view of digital subtraction angiography of the right internal carotid artery showing an aneurysm associated with a duplicated middle cerebral artery and anterior choroidal artery. *: aneurysm. **(D)** Fusion three-dimensional computer graphics integrating MR imaging/MR angiography and three-dimensional rotational angiography. Fusion three-dimensional computer graphics showed that the duplicated middle cerebral artery and the anterior choroidal artery originated from the dome. *: aneurysm; small arrow (green): duplicated middle cerebral artery; arrowhead (blue): anterior choroidal artery; large arrowhead (yellow): posterior communicating artery. **(E)** Fusion three-dimensional computer graphics. Fusion three-dimensional computer graphics shows that the duplicated middle cerebral artery passed through the sylvian fissure along the M1 segment of the MCA. *: aneurysm; small arrow (green): duplicated middle cerebral artery; arrowhead (blue): anterior choroidal artery; large arrowhead (yellow): posterior communicating artery. **(F)** Fusion three-dimensional computer graphics. Fusion three-dimensional computer graphics showed that the duplicated middle cerebral artery perfused the anterior temporal lobe. *: aneurysm; small arrow (green): duplicated middle cerebral artery. Fusion three-dimensional computer graphics were reconstructed by GRID 1.1 software (Kompath Inc., Tokyo, Japan).

DISCUSSION

To our knowledge, this is the first report of an ICA aneurysm with a DMCA and the AChA arising from the dome that was successfully treated without complications. Here, we discuss the anatomical aspects of this aneurysm and the importance of preserving the incorporated branch vessels.

The incidence of DMCA ranges from 0.7 to 2.9% (9, 10). The DMCA arises between the origin of the AChA and the distal end of the ICA. Both the AChA and MCA originate from the cranial division of the ICA, and the AChA is embryologically earlier than the MCA (11). Komiyama et al. (1) described the

DMCA as an anomalous early ramification of the early branch of the MCA, which originates from the distal end of the ICA. DMCA is classified into two types, A and B, based on the point of origin. A Type A DMCA arises from the top of the ICA, while a Type B DMCA originates from the ICA between the AChA and proximal portion of the ICA bifurcation (12, 13). Most DMCA aneurysms are type B (5, 14). To the best of our knowledge, 42 cases of DMCA aneurysms have been reported (4, 5, 15–21). Most of these aneurysms are IC-DMCA aneurysms of Type B DMCA. There were five cases of rare variations among the DMCA aneurysms (**Table 1**) (15, 21–24), including three cases of aneurysms on DMCA. Theoretically, aneurysms that involve AChA, A1, or M1 could be considered as DMCA aneurysms; however, aneurysms that involve AChA, as in the present case, were not detected. Kai et al. (13) estimated that type B DMCA is exposed to higher hemodynamic stress because the angle between the ICA and type B DMCA is sharper than that of type A. Moreover, previous studies have reported that aneurysms associated with type B DMCA are at a high risk of rupture even if they are small in size. Therefore, aggressive treatment could be considered for such aneurysms, as in our case (13, 17, 25).

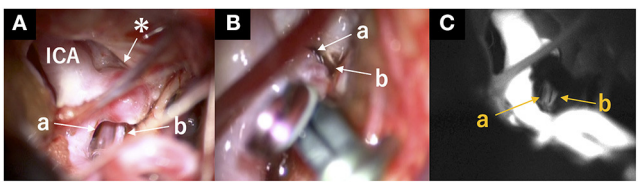

FIGURE 2 | Intraoperative view. **(A)** Intraoperative view indicated the structures surrounding the aneurysm before clipping. *: aneurysm; a: anterior choroidal artery; b: duplicated middle cerebral artery. **(B)** Two titanium clips were combined and applied to occlude most part of the aneurysm, while confirming the patency of the DMCA and the AChA. a: Anterior choroidal artery; b: duplicated middle cerebral artery. **(C)** Patency of the duplicated middle cerebral and anterior choroidal arteries was confirmed using indocyanine green video angiography after clipping. a: anterior choroidal artery; b: duplicated middle cerebral artery.

The differential diagnosis of ICA aneurysm with DMCA and AChA arising from the dome included an aneurysm that involves the double AChA. According to Lasjaunias (26), the origin of the AChA is located posterolateral to the supracavernous portion of the ICA, between the posterior communicating artery and the ICA bifurcation. The AChA passes posterolaterally above the medial part of the uncus, along the optic tract, and laterally curves to reach the lateral geniculate body in the cisternal segment. Usually, the AChA gives off one or two branches that terminate at the medial wall of the temporal lobe. Double AChAs were found in 4–13% of cases (27–29), and their origins were classified into two types. One consists of two separate arteries arising from the ICA, and the other arises from the ICA as a single artery but immediately divides into two trunks. If there are double AChAs, the more distal branch terminates in the medial temporal lobe and the more proximal branch nourishes the remaining anterior choroidal field (29). Aneurysms involving a double AChA, which appear similar to the images of our case, have been reported (30, 31). Generally, the DMCA runs through the sylvian fissure and supplies the anterior and/or middle temporal territories (1). The present case is thought to be a DMCA because the artery originated between the AChA and the distal end of the ICA, passed through the sylvian fissure along the M1 segment of the MCA and perfused the anterior temporal lobe. Embryologically, the DMCA cannot originate proximal to the AChA because the AChA appears earlier in development. Uchino et al. (32) reported a case of DMCA arising from the origin of the AChA. In that case, the common origin of the DMCA and AChA was confirmed, and infundibular dilatation was indicated in the ICA-AChA-DMCA junction. It is assumed that the aneurysm in this case was the result of a DMCA aneurysm involving the AChA, an AChA aneurysm involving a DMCA, or an aneurysm occurring at the common origin of a DMCA and the AChA.

Miyoshi et al. reported a case of aphasia after clipping a DMCA aneurysm (20). DMCAs frequently involve perforating arteries (9, 33). In addition, a DMCA can potentially supply collateral blood flow to the MCA territory in cases of MCA occlusion (34). Thus, blood flow in the DMCA should

TABLE 1 | Rare variations of DMCA aneurysms.

Year	References	Age (years)	Sex	Size	Onset type	Case presentation	Treatment
2004	Uchino et al. (22)	45	F	N/A	Ruptured	Saccular AN originated from DMCA trunk	Clipping
2010	Otani et al. (23)	66	F	5–10 mm	Ruptured	ICA AN at the origin of DMCA associated with accessory MCA and MCA aplasia	Clipping
2011	Takahashi et al. (24)	62	F	<5 mm	Ruptured	Kissing AN of ICA: ACHA was situated between two AN and DMCA originated from distal AN	Coiling
2012	LaBorde et al. (21)	34	M	10 mm	Unruptured	Fusiform AN originated from DMCA trunk	Trapping + STA-DMCA bypass
2018	Mori et al. (15)	62	M	<5 mm	Unruptured	Saccular AN originated from DMCA trunk	Observation

AChA, anterior choroidal artery; AN, aneurysm; DMCA, duplicated middle cerebral artery; ICA, internal cerebral artery; MCA, middle cerebral artery; N/A, not assessed; STA, superficial temporal artery.

be preserved. Furthermore, ischemia of the territory of the AChA causes severe neurological deficits (35, 36). Friedman et al. (37) showed that the AChA originates from the dome in 18% of AChA aneurysms, and the ischemic complication rate associated with treatment was even higher in such cases. As mentioned above, when treating aneurysms with a DMCA and the AChA originating from the dome, preserving these important branching vessels should be considered.

CONCLUSION

To the best of our knowledge, this is the first report of an ICA aneurysm with a DMCA and the AChA arising from the dome. In such cases, the anatomy of the DMCA and AChA must be well-characterized before treatment is initiated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

SM certifies that all authors have participated and have been involved in the cases presented and/or in the elaboration of the present manuscript. All authors contributed to the article and approved the submitted version.

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CASE REPORT
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Extracranial Vertebral Artery-Internal Jugular Vein-Spinal Vein Fistula in Neurofibromatosis Type I: Case Report and Literature Review

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Background: A cervical arteriovenous fistula (AVF) in neurofibromatosis type I (NF-1) is uncommon, and it brings challenges and difficulty in treatment.

Case Presentation: A 39-year-old woman was diagnosed with an NF-1-associated spontaneous vertebral artery-internal jugular vein-spinal vein fistula. The fistula was placed by coil embolization. Postoperative examination showed that the fistula closure was satisfied, and the patient's abnormal clinical manifestation disappeared without any complications after 24 months of interventional embolization. As per the literature, interventional embolization is currently the main treatment method, and it has the distinguishing features of less trauma, quick recovery, and a good prognosis.

Conclusion: NF-1 associated with a spontaneous arteriovenous fistula is rare in clinical practice, which carries significant challenges in treatment, but can be effectively treated using endovascular embolism. Endovascular embolism could be the potential choice of treatment in NF-1 associated with AVF.

Keywords: arteriovenous fistulas, neurofibromatosis type I, embolization, fistula, interventional therapy

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INTRODUCTION

Neurofibromatosis type 1 (NF-1) is an autosomal dominant familial neurocutaneous disease, and it accounts for about 1/3,000 (1). NF-1 is also known as von Recklinghausen's disease and is caused by mutations in the tumor suppressor gene NF-1 (17q11.2) (2–4), which encodes neurofibromin that can activate cell proliferation *via* downregulating the Ras-Raf/MAPK signaling pathway (5). It is characterized by multiple café au lait macules (CALMs) on the skin, i.e., pigmented patches, multiple neurofibromas of the peripheral nerve, and optic pathway gliomas (OPGs) (6). Occasionally it is complicated by vascular diseases, such as vascular stenosis, occlusion, aneurysms, and arteriovenous fistulas, which are relatively rare (7–13).

It is well known that the incidence of congenital vascular malformations is very low, whereas the number of NF-1-related vascular abnormalities is higher. Its rate of occurrence is 0.4 to 6.4% (14–16) and is mainly found in the aorta and renal arteries (17). Patients suffering from cervical arteriovenous fistulas (AVFs) associated with NF-1 are very rare (18), and this is usually developed

from trauma and medicine. The etiology of NF-1-related AVF remains unclear (18), and treatment is facing serious challenges.

Here, we reported one case of a vertebral artery-internal jugular vein-spinal vein fistula with NF-1 and gave a general view of the existing works of literature in this article.

CASE PRESENTATION

A 39-year-old woman with NF-1 for 32 years was admitted to our hospital with the complaint of the existence of a left cervical mass with tremors for 8 years without any inducement. Physical examination demonstrated multiple subcutaneous masses in different sizes and CALMs scattered all over the body (**Figure 1**). A neck mass approximately 4 × 3 cm in size was palpable on the left side of the neck, with a hard texture, poor mobility, active tremor, and continuous mechanical vascular murmur. The strength of the left limb muscle was weakened with a grade of III. Pathologic signs examination indicated the bilateral Babinski sign and positive patellar and left ankle clonus. MRI showed abnormal signals on the left side of the neck and the spinal canal of the neck. Arteriovenous malformations, neoplastic dilatation, and thrombosis were observed on the left side of the neck, also, a few blood vessels were found to protrude into the spinal canal to compress the cervical spinal cord (**Figure 2**). Three-dimensional CT showed an enlarged diameter of the V2 segment of the left vertebral artery that communicated with the internal jugular vein and spinal cord vein. The corresponding diameter was significantly enlarged, and the spinal cord of the C2-C5 vertebral segments was significantly compressed. It revealed the left vertebral artery-internal jugular vein-spinal vein fistula (**Figure 3**). Vertebral angiography showed a dilated left vertebral vein at the later stage of the artery, and hence, an arteriovenous fistula was considered (**Figure 4**). Before embolization, the angiogram showed multiple fistulas (**Figure 5A**) and three 8–12 double-plug spring coils. One 8 mm × 20 cm controllable spring coil and another 6 mm × 20 cm controllable spring coil [Axium MicroFX Coils (ev3; Plymouth, Minnesota, USA)] were applied to the main part of the fistula (**Figure 5B**). During the angiography, post-placement of the spring coils revealed significant occlusion, and vein development was greatly reduced compared to before (**Figure 5C**). After the coil embolization, 24-month follow-up demonstrated significantly improved muscle strength of the left limb with a grade of IV to V, though it was still slightly abnormal compared to the right limbs, and the abnormal numbness of the left upper limb disappeared fully.

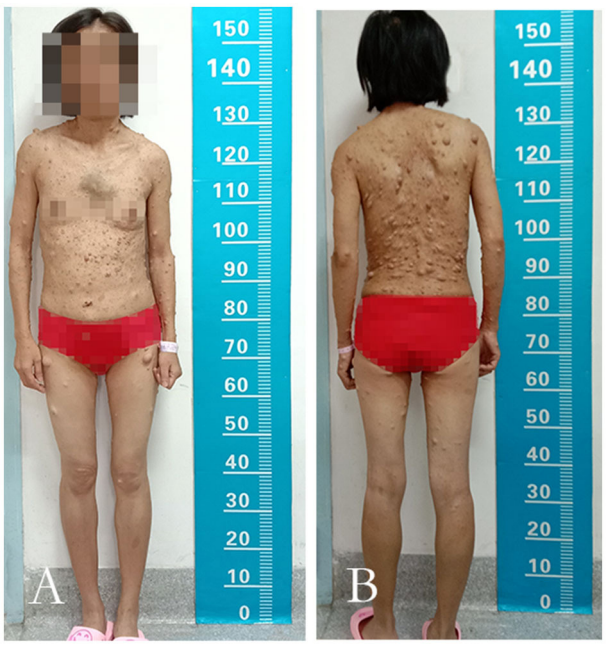

FIGURE 1 | The anterior view and the posterior view of the patient. **(A,B)** The image showed innumerable masses spread throughout her body and mainly concentrated on the face, neck, bilateral upper limbs, and trunk.

DISCUSSION

NF-1 is known as an autosomal dominant familial genetic disease, which partly occurs due to genetic mutations in all ethnic

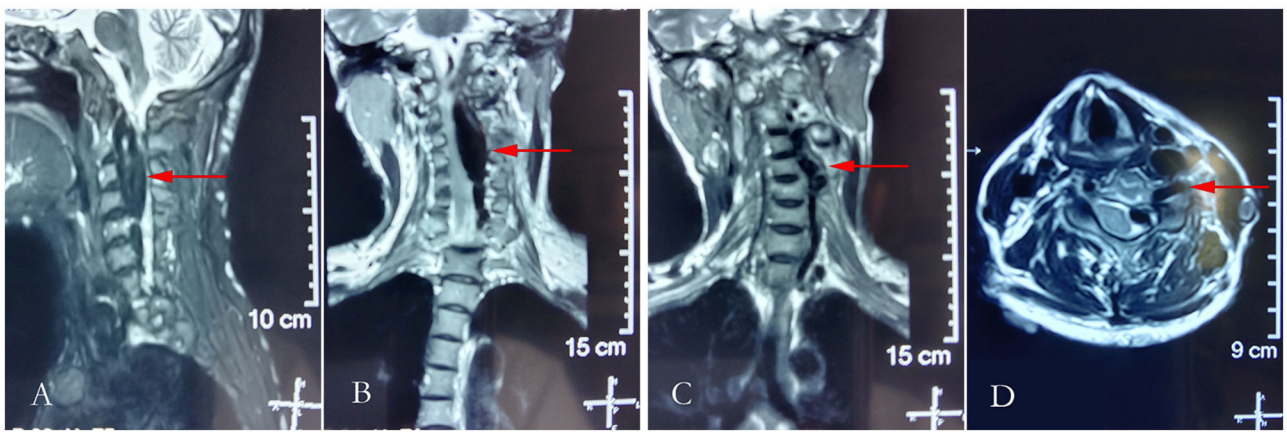

FIGURE 2 | Cranial T2-weighted magnetic resonance imaging. **(A)** Sagittal plane of the neck; **(B,C)** the coronal plane of the neck; and **(D)** horizontal plane of the neck.

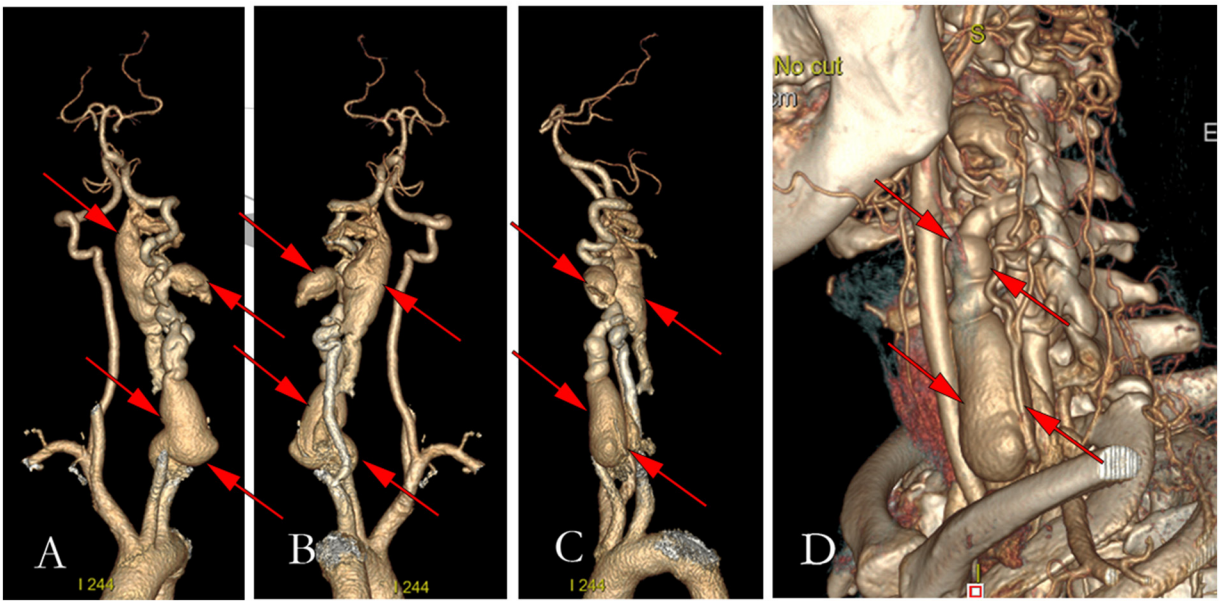

FIGURE 3 | Figures of preoperative three-dimensional computerized tomography. **(A)** The anterior view of the three-dimensional CT of vertebral arteriography; **(B)** The left view of the three-dimensional CT of vertebral arteriography; **(C)** The post view of the three-dimensional CT of vertebral arteriography; **(D)** Three-dimensional reconstruction of the left neck.

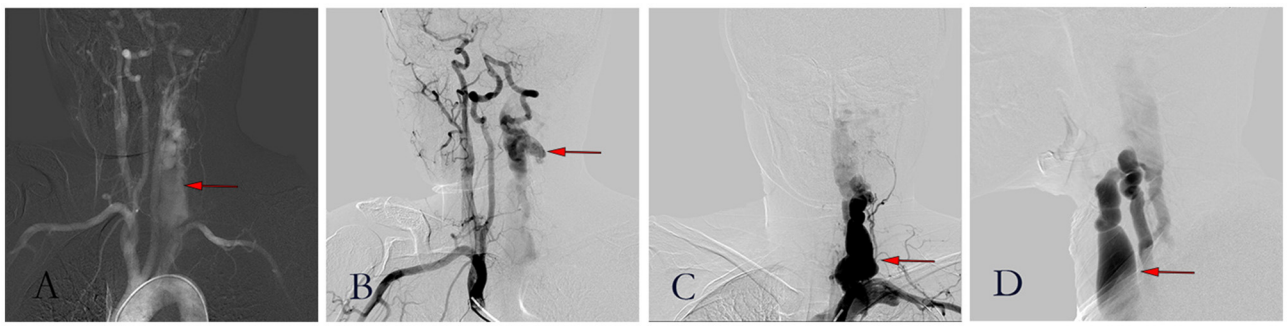

FIGURE 4 | Figures of digital subtraction angiography. **(A)** Angiography showed a large area of the left vertebral artery; **(B)** Brachiocephalic trunk angiography showed a large flow of blood from the right vertebral artery through a circle of Willis to the left; **(C)** Posterior-anterior image of left vertebral arteriogram; **(D)** Lateral image of left vertebral arteriogram.

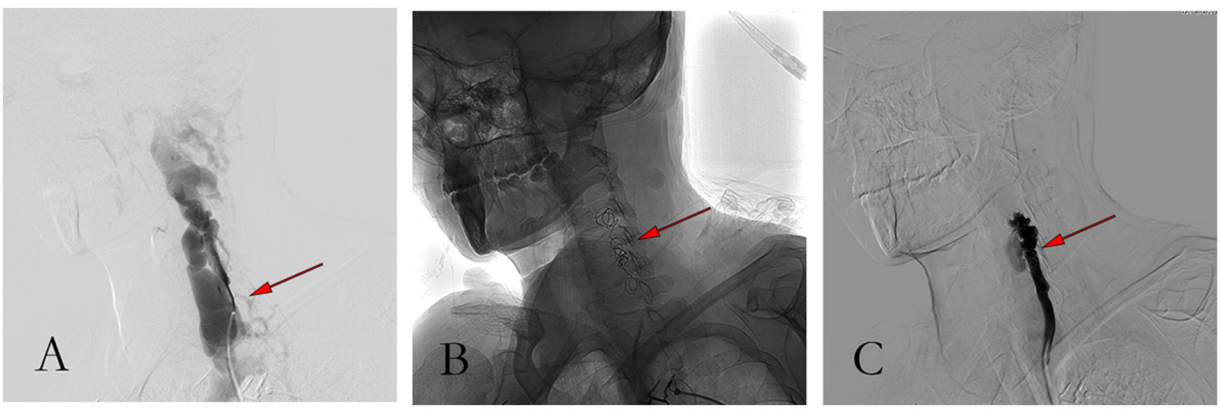

FIGURE 5 | Pictures of the procedure. **(A)** Angiography showed massive venous development before embolization; **(B)** Angiographic image after coil embolization; **(C)** Angiography showed good occlusion and less vein development after coil embolization.

groups (3). In our case report, the patient was diagnosed with neurofibromas by pathological examination in another hospital when she was young and denied any family member had the same clinical manifestation. NF-1 connected with a spontaneous arteriovenous fistula is very uncommon in clinical practice.

In the literature, there were 49 cases of AVF associated with NF-1, including our report. Moreover, spontaneous AVF takes up the majority of all cases, about 40 cases. Among the remaining cases, four cases had a history of operation, and five cases had trauma. NF-1-associated spontaneous AVF cases occurred more in women, accounting for approximately 78.38% compared to 24.32% in men, see **Table 1**, whereas in the two cases, gender remained unidentified. The average age of spontaneous AVF in NF-1 was 38.77 years (39.47 ± 14.02 years), with a maximum age of 70 years old (19), while the youngest suffering from the disease had just been born (20). Additionally, spontaneous AVF occurred significantly in the neck, in approximately 77.5% (31/40), which does not match with previous reports (17). However, AVF took place in the head in approximately 10% (4/40) of cases, and the chest in 5% (2/40) of cases. Along with this, spontaneous AVF occurred on the left side and right side in 58.33% (21/36) and 33.33% (12/36) of cases, respectively, while two cases had bilateral spontaneous AVF.

The exact pathogenesis of abnormal blood vessel appearance associated with NF-1 remains unclear. Deans (21) thought that vascular smooth muscle dysplasia results from the attenuation of intimal hyperplasia or arterial wall cell proliferation, which leads to the weakening of the arterial tube wall, aneurysm, and artery ruptures which eventually connect to the adjacent veins. Alternatively, arteriovenous malformations are due to mesoderm dysplasia. Riccardi hypothesized that the expression of neurofibromin in endothelial and smooth muscle cells of blood vessels would change due to the mutation of the NF-1 gene, and the maintenance effect of neurofibromin on blood vessels would be lost (22), eventually leading to inflexible blood vessels. In the literature, there were 80% of patients (32/40) with pure NF-1-related spontaneous AVF and 20% of patients (8/40) with both aneurysms and spontaneous AVF.

AVF with NF-1 is rare in clinical practice, though there is no difficulty in diagnosis with CT angiography (CTA) (23), magnetic resonance angiography (MRA) (24), and digital subtraction angiography (DSA). However, still, there are challenges and difficulties for good treatment. The purpose of treatment is to completely seal the fistula. Alternative treatments include traditional open surgery (ligation, reconstruction, etc.) and interventional embolization (balloons, coils, tissue glue, vinyl alcohol polymers, etc.) (25–30). However, whether it is traditional open surgery or interventional embolization, vascular fragility associated with NF-1 brings great risk to treatment, viz., rupture of blood vessels and bleeding. Compared with surgical treatment, the initial failure rate and recurrence rate were higher (31, 32). However, with the advancement of endovascular embolization materials and surgical techniques, the success rate of intravascular interventional therapy has greatly improved (31–33). In addition, interventional therapy has certain features, such as less damage, higher safety, and quick recovery after treatment (29, 34–36). Therefore,

TABLE 1 | Summary of clinical information of spontaneous arteriovenous fistula with neurofibromatosis.

	Gender			Position					Side			Aneurysm		Treatment								
														Op			Em			Op and em		
	M	F	NA	H	N	T	H and N	NA	L	R	B	NA	Yes	NO	Re	Ot	NA	Re	De	NA	Re	NA
	9	29	2	4	31	2	1	2	21	12	3	4	8	32	3	1[#]	1	25	2*	1	4	3
To*	40			40					40				40			5			28		4	3

*M, male; F, female; NA, not available; H, head; N, neck, T, thorax; Ot, other; L, left; R, right; B, bilateral; Op, operative; Em, embolization; Re, recovery; De, dead; To, total. [#]The patient left with neck pain and post-laminectomy kyphotic deformity. *One patient died from pneumonia.*

endovascular interventional therapy is undoubtedly the best choice.

Detachable balloons are best suited for fistula occlusion as they can be inflated and contracted repeatedly before separation to achieve precise fistula placement and optimal occlusion. However, if the balloon is deflated, it can result in recurrence of the fistula, and thus, it is rarely used in embolization. Particulate or liquid embolic agents are not feasible for AVF, as there are likely to be swept away by rapid flow without blocking the fistula and cause accidental embolization in other blood vessels. The detachable coil attracts negatively charged blood components (red blood cells, white blood cells, platelets, etc.) to electro-coagulate, forming a thrombus in the vessel. Due to its good circling compliance, the coil can be adjusted if the position is not satisfied and shows advantages to embolization.

In our case, if open surgery is performed, it is necessary to cut the vertebral artery foramen, lamina, etc., which is more traumatic and may affect the stability of the spine. DSA demonstrated that the fistula had a dual vascular nutrient supply, i.e., from the left vertebral artery and the right vertebral artery through to the cranial base artery ring. Occlusion *via* the retrograde approach is extremely difficult and risky, as it has to travel along the long and inward-curving vascular skull. Thus, occlusion was achieved through an antegrade approach (37) using coils. After the placement of the spring coil, the angiography showed that adequate occlusion was achieved. After 24 months of follow-up, the patient's symptoms and signs disappeared, which indicated that the treatment we chose had a favorable outcome. However, there is no standard for endovascular treatment which is recognized as excellent.

There are many methods of endovascular embolization for the treatment of AVF. Embolic agents can vary, such as balloons, coils, tissue glue, and vinyl alcohol polymers, as per the size of the fistula or different hemodynamics. Along with all the advancements and benefits of the embolization process, downside factors, such as the occurrence of new arteriovenous fistulas or rupture of blood vessels, should be considered. These secondary damages take place as the blood vessels are fragile.

CONCLUSION

In clinical practice, the occurrence of NF-1 associated with spontaneous arteriovenous fistula is very uncommon. It mostly occurs in female patients and often in the left blood vessel. Literature findings illustrated that endovascular embolization treatment has noticeable benefits.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

JiaC, JieC, and TL performed the research and wrote the paper. JiaC, JieC, TL, and JJ designed the research study. TC, HL, and CL contributed essential reagents or tools. JiaC, JieC, and CL analyzed the data. JieC, JinC, and XZ reviewed the manuscript. All authors have read and approved the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2022.855924/full#supplementary-material

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CASE REPORT
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Case Report: Stent Retriever Thrombectomy of Acute Basilar Artery Occlusion *via* the Type 1 Proatlantal Intersegmental Artery

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Stent retriever thrombectomy (SRT) is one of the most effective methods for the recanalization of acute basilar artery occlusion (ABAO). The proatlantal intersegmental artery (PIA) is a rare carotid-vertebrobasilar anastomosis. Recognition of this rare form of anastomosis is particularly important for the rapid establishment of positive blood flow in patients with ABAO. In this case, the patient had a rare, left type 1 PIA. The right vertebral artery (VA) was tenuous and did not enter the cranium. We performed a thrombectomy of the ABAO by inserting a catheter *via* the type 1 PIA. The complete recanalization of basilar artery (BA) flow was achieved following two stent retractions; however, the patient eventually died of brain stem hemorrhage.

Keywords: proatlantal intersegmental artery, acute basilar artery occlusion, thrombectomy, stroke, case report

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INTRODUCTION

Acute basilar artery occlusion (ABAO) is the most serious type of acute ischemic stroke (AIS). Failure to achieve rapid vascular recanalization can lead to high mortality and disability rates and a poor clinical prognosis. The safety and efficacy of stent retriever thrombectomy (SRT) in the treatment of acute large vessel occlusion (LVO) in the anterior circulation have been confirmed in many large clinical trials (1). In recent years, SRT has been attempted for the treatment of ABAO, which has been rigorously evaluated and has achieved good results (2).

The proatlantal intersegmental artery (PIA) is a rare carotid-vertebrobasilar anastomosis (CVA) that is often accompanied by vertebral artery (VA) and posterior communicating artery hypoplasia and is the main blood supply for the vertebrobasilar artery (3). In this case, the patient had a rare, left type 1 PIA. We did not perform a preoperative CT angiography (CTA) examination to assess vascular conditions, which led to some difficulties in identifying effective catheter access during the emergency thrombectomy.

CASE DESCRIPTION

A formerly healthy, 33-year-old man presented to our emergency department 6 h after the onset of unconsciousness. The patient had no history of hypertension, diabetes mellitus, or cardiovascular disease. Upon admission, neurological examination revealed a severe disturbance of consciousness with a Glasgow Scale (GCS) score of 4 (E1V1M2). The bilateral pupil size was about 1.5 mm, and light reflex was absent. When the patient was subjected to intense painful stimuli, the limbs were hyperextended. Bilateral pathological signs were not elicited. His initial National Institutes of Health Stroke Scale (NIHSS) scores were 39.

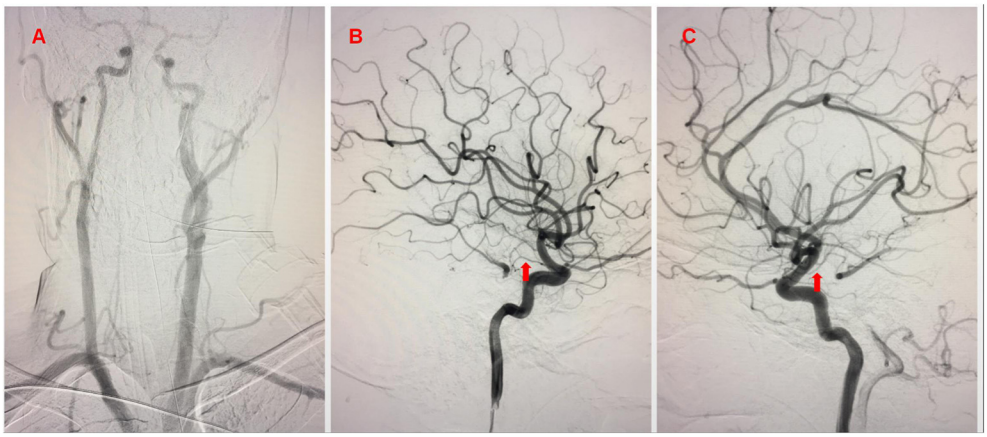

FIGURE 1 | (A) Aortic arch catheter angiogram showing the right vertebral artery (VA) was tenuous and did not enter the skull; the left VA was absent. **(B,C)** Lateral internal carotid artery (ICA) catheter angiogram showed that bilateral posterior communication arteries were stunted (arrow) and collateral circulation was poor.

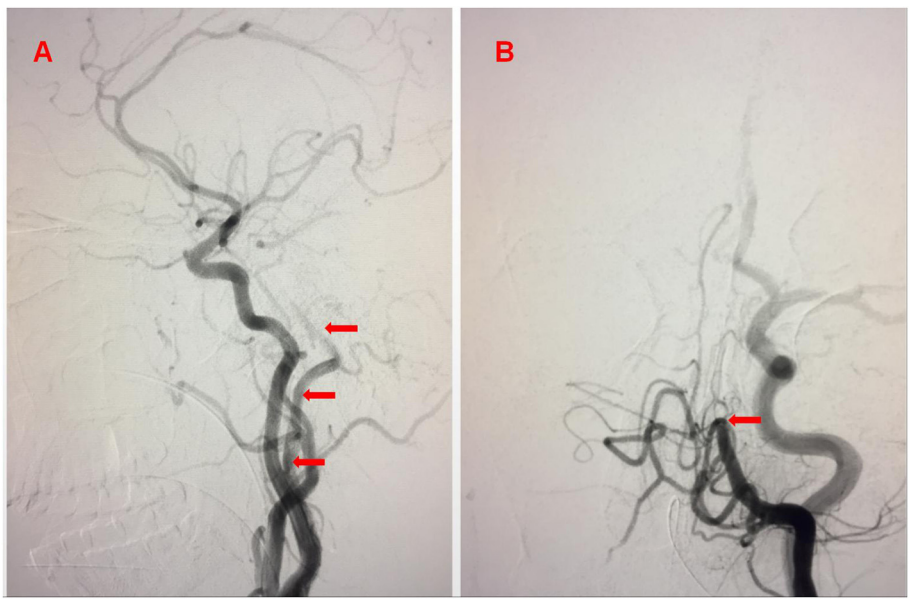

FIGURE 2 | (A) Lateral ICA catheter angiogram showing a large collateral vessel [type1 proatlantal intersegmental artery (PIA)] was found emanating from the carotid segment of the ICA (arrow). **(B)** Angiography *via* type1 PIA demonstrated the basilar artery (BA) occluded far from the anterior inferior cerebellar artery (arrow).

Non-contrast head CT demonstrated no significant infarction or cerebral hemorrhage. Due to problems with the picture archiving and communication system (PACS) in the hospital, CTA and MRI examinations were not performed. We were concerned that moving the patient to another hospital could delay optimal treatment. The combination of clinical symptoms and a physical examination of the nervous system led to a clinical diagnosis of AIS of the posterior circulation. He was taken for a thrombectomy.

We performed emergency digital subtraction angiography (DSA). The aortic arch catheter angiogram showed that the patient's right VA was tenuous and did not enter the skull; the left VA was absent. The lateral internal carotid artery (ICA) catheter angiogram showed that the bilateral posterior communication arteries were stunted, and that collateral circulation was poor (**Figure 1**).

During the left common carotid artery (CCA) angiography, a large collateral vessel (type 1 PIA) was found emanating from the carotid segment of the internal carotid artery (ICA). The angiographic catheter was placed at the beginning of this abnormal collateral vessel, and we saw that this vessel rose vertically and continued into the left vertebrobasilar artery. The BA was occluded far from the anterior inferior cerebellar artery (**Figure 2**).

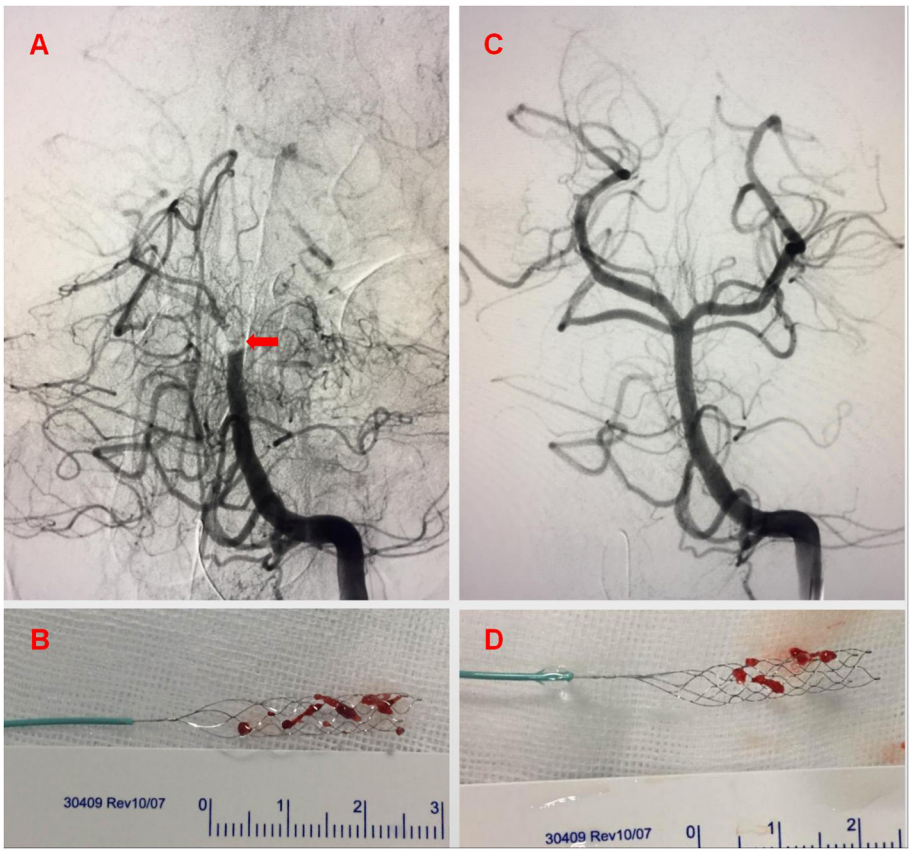

FIGURE 3 | Some residual thrombus remained at the top of the basilar artery **(A)** after the first retrieval of the thrombus with stent **(B)** (arrow). After the second retrieval of the thrombus **(D)**, the basilar artery perfusion recovered completely **(C)**.

TREATMENT

A 6 mm × 30 mm Solitaire stent was chosen for mechanical thrombectomy *via* the type 1 PIA. The complete recanalization of BA flow was achieved following two stent retractions, reaching thrombolysis in cerebral infarction (TICI) level 3 (**Figure 3**). Immediate post-operative head CT showed brain stem hemorrhage. The patient was returned to NICU with an oral trachea cannula. The systolic blood pressure was strictly controlled. Since the patient's autonomous respiration was weak and oxyhemoglobin saturation was difficult to maintain, we gave the patient assisted mechanical ventilation and other related treatments.

OUTCOME AND FOLLOW-UP

The patient eventually died of a brain stem hemorrhage.

DISCUSSION

During the early development of the human embryo, there are various anastomotic channels between the carotid artery and the vertebrobasilar artery system (4). In most cases, CVAs usually regress during embryonic development. However, there are rare cases in which these original anastomoses do not disappear, but rather persist into adulthood. These are known as the persistent primitive PIA, the persistent hypoglossal artery (PHA), the persistent auricular artery (PAA), and the persistent trigeminal artery (PTA).

Proatlantal intersegmental artery is a rare CVA with an incidence of ∼0.02% (5). The PIA is divided into two types according to two differing origins. Type 1 PIA originates from the dorsal cervical segment of the ICA at the level of the C2-3 vertebra of the cervical spine. Type 2 PIA originates from the initial part of the external carotid artery at the level of the C2-3 vertebra of the cervical spine. Both types of PIA travel upward and enter the skull through the foramen magnum. PIA is often associated with a transient ischemic attack (TIA), vertebrobasilar insufficiency (VBI), and even cerebral hemisphere or posterior circulation infarction (3).

Type I PIA and PHA are easily confused because they both originate from the extracranial segment of the ICA. The main differences between these two vessels are as follows: (1) PHA originates from the level of the C1 vertebra of the ICA or the C1-2 intervertebral space, which is higher than that of type I PIA; (2) PHA has a longer vertical lift than type 1 PIA; (3) type

I PIA enters the cranium through the foramen magnum, while PHA enters the cranium through the sublingual neural tube (4). Park JS et al. recently reported a case of acute basilar artery occlusion treated with Endovascular thrombectomy *via* PHA (6). In our case, a primitive anastomotic artery had originated from the dorsal part of the cervical segment of the left ICA and the upper part of the mandibular angle (at the level of the C2-3 vertebral body); this had moved upward and entered the skull through the foramen magnum. Therefore, we speculated that the primitive anastomotic artery was a type 1 PIA (not confirmed by three-dimensional CTA).

Good collateral circulation and distal BAO are known to be independent predictors of clinical outcomes after intravascular treatment in patients with ABAO (7). Montechiari et al. reported a case of type 1 PIA associated with an ipsilateral embryonal posterior cerebral artery in 2013 (8). However, the patient's bilateral posterior communication arteries were stunted. Although the BA was completely recanalized by SRT and blood perfusion was at TICI level 3, the patient's poor collateral circulation may have resulted in a very poor prognosis even in the absence of a fatal brain stem hemorrhage.

CONCLUSION

Proatlantal intersegmental artery itself does not require treatment; however, because of its special anatomy, the vertebrobasilar system must share blood flow with the carotid system. Thus, PIA may be associated with a higher incidence of posterior circulation ischemic events. Cranio-carotid CTA examination is particularly important for ABAO, especially when ABAO is combined with PIA and other rare vascular variants.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) and/or minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

LZ, LY, XL, XW, GZ, and JW contributed to the conception and design, acquisition and interpretation of the case data, drafting and revising of the article critically for important intellectual content, final approval of the version published, and agreement to be accountable for the accuracy or integrity of the article. All authors contributed to the article and approved the submitted version.

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