Case Report

Management of Direct Internal Carotid-Cavernous Sinus Fistula in a Patient with Ehlers–Danlos Syndrome: A Case Study on Selective Transvenous Embolization Using Coils and *N*-Butyl-2-Cyanoacrylate

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Objective: Direct carotid-cavernous fistula (CCF) is a common neurovascular complication associated with Ehlers–Danlos syndrome (EDS). Nevertheless, reports indicate a significant incidence of treatment-related complications.

Case Presentation: We present a case of right CCF in a 28-year-old female with EDS. Femoral artery and vein punctures were performed under ultrasound guidance. We executed transvenous embolization (TVE) of the draining veins and the shunted fistula using a combination of coils and *n*-butyl-2-cyanoacrylate (NBCA), facilitated by an assisted transarterial balloon. The CCF resolved without any procedural complications.

Conclusion: Utilizing a combination of coils and NBCA in TVE is seen as a safe and efficient method for addressing CCF in patients with EDS. It enables preserving better visualization of the cavernous sinus and adjacent structures, making this approach particularly effective. By keeping a close watch, monitoring for potential high-risk complications, and strategically placing devices between the arterial and venous sides, the arterial puncture profile is reduced, enabling safer endovascular treatment.

Keywords direct carotid-cavernous fistula, vascular Ehlers–Danlos syndrome, transvenous embolization

Introduction

Ehlers–Danlos syndrome (EDS) encompasses a variety of autosomal dominant connective tissue disorders that involve abnormalities in collagen production. Patients often face vascular fragility that can lead to aneurysms and arterial ruptures. One common neurovascular complication linked to EDS is direct carotid-cavernous fistula (CCF). In the 1990s, interventional radiology (IVR) was deemed contraindicated for EDS due to its substantial complication rates (22%–35%) and mortality rates (6%–12%).[1)] Recently, multiple cases have reported successful IVR treatments; however, there have also been instances of procedure-related deaths.[2)] We present a case of CCF associated with EDS, where we achieved complete obliteration of the shunt using transvenous embolization (TVE) supplemented with a transarterial approach.

Case Presentation

A 28-year-old woman arrived at our hospital experiencing sudden pain and swelling in her left leg. She was diagnosed with a ruptured left posterior tibial artery aneurysm and underwent coil embolization under general anesthesia. After extubation, the patient experienced pain in her

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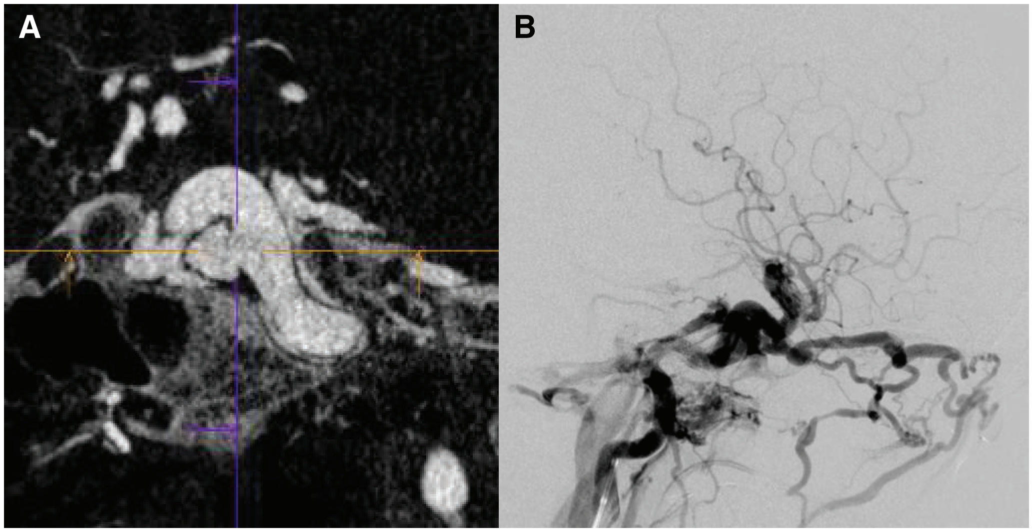

Fig. 1 Imaging findings in right ICA aneurysm and associated fistula. (**A**) Sagittal view of the 3D rotational angiography of the right ICA, revealing an aneurysm-like structure in the anterior wall of the cavernous segment. (**B**) Preoperative DSA (anterior view and lateral view) showing right CCF draining anteriorly into the right SOV, IOV, and pterygoid plexus via FOEV, as well as posteriorly into the UV, IPS, prepontine BV, and ICS. BV, bridging vein; CCF, carotid-cavernous fistula; FOEV, foramen ovale emissary vein; ICA, internal carotid artery; ICS, intercavernous sinus; IOV, inferior ophthalmic vein; IPS, inferior petrosal sinus; SOV, superior ophthalmic vein; UV, uncal vein

right eye and a right subconjunctival hemorrhage. A retinal tear was diagnosed in the ophthalmology department, and laser coagulation was performed. Two weeks after surgery, she developed right abducens nerve palsy and reported tinnitus in her right ear. A MRA revealed a right CCF, prompting her referral to the neurosurgery department for further assessment. The patient also presented with physical characteristics, including micrognathia, a curved right fifth toe, skin hyperextensibility with visible veins, atrophic scarring, and joint hypermobility. No other vascular abnormalities or malformations were observed, and there was no family history suggestive of vascular fragility or any reported developmental abnormalities. Given these features, she received a diagnosis of EDS and related CCF, leading to a plan for TVE.

Given the patient's vascular fragility, a femoral puncture was conducted with ultrasound guidance. A 5-Fr 25-cm sheath was inserted into the right femoral artery, while an 8-Fr, 25-cm sheath was placed into the right femoral vein. Preoperative DSA showed a fistula situated on the anterior wall of the cavernous segment of the right internal carotid artery (ICA). Additionally, a saccular aneurysm-like structure measuring about 5 mm in maximum diameter was found within the cavernous sinus (CS) (**Fig. 1A**). Shunt flows from the right CS were draining into the uncal vein (UV) and the pterygoid plexus via the foramen ovale emissary vein (FOEV), as well as the superior ophthalmic vein (SOV), inferior ophthalmic vein (IOV), inferior petrosal sinus (IPS), prepontine bridging veins, and intercavernous sinus (ICS) (**Fig. 1B**).

The lesion was identified as a type A CCF as per the Barrow classification.[3] A 5-Fr Selecon MP balloon catheter 2 (Terumo, Tustin, CA, USA) was used for navigating the right ICA to inject the contrast medium and manage flow with the balloon. To block the draining veins and embolize the aneurysmal structure at the fistula, TVE was carried out. An 8-Fr Roadmaster catheter (Nipro, Osaka, Japan) was placed in the right internal jugular vein (IJV), allowing for selective catheterization of each vein. The TACTICS catheter (Technocrat, Aichi, Japan) was chosen as the intermediate catheter, which was positioned in the right CS through the right IPS. The Headway 17 microcatheter (Terumo) was then guided to the draining veins using the Chikai microguidewire (Asahi Intecc, Aichi, Japan). Embolization was executed with a combination of coils and 20% *n*-butyl-2-cyanoacrylate (NBCA), deploying 2 coils in the UV, 3 in the SOV and IOV, and 2 in the FOEV (**Fig. 2A** and **2C**).

The aneurysm at the fistula site was embolized with 6 coils, without specific flow control measures. (**Fig. 2B** and **2C**) While minimal antegrade flow to the IPS persisted, no retrograde flow into intracranial veins, such as the bridging vein (BV) or superior petrosal sinus, occurred. The procedure was subsequently concluded (**Fig. 3A**). Immediately

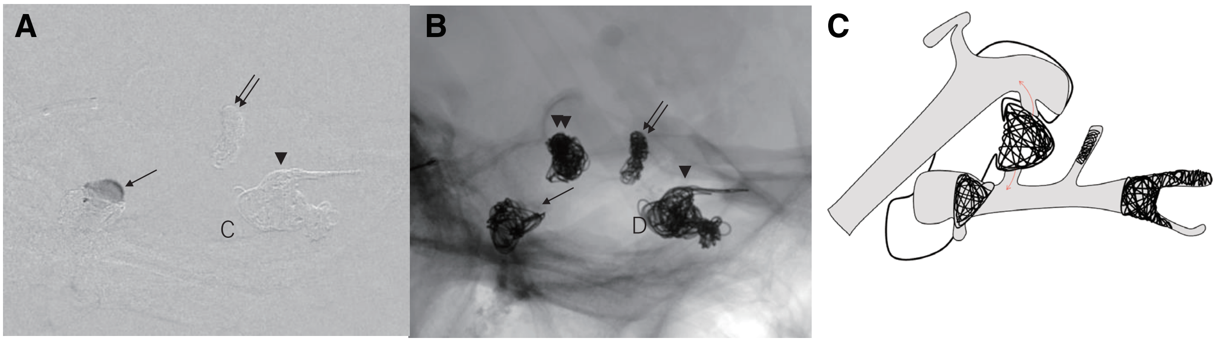

Fig. 2 DSA results and schematic overview during TVE. (**A**) Selective embolization of the FOEV was performed using coils and NBCA. (Notable vessels include FOEV, arrow; UV, double arrow; and SOV and IOV, arrowhead). (**B**) Final angiographic view after transvenous embolization, highlighting an aneurysm-like structure (double arrowhead). (**C**) Schematic representation of the CS and ICA. CS, cavernous sinus; FOEV, foramen ovale emissary vein; ICA, internal carotid artery; IOV, inferior ophthalmic vein; NBCA, *n*-butyl-2-cyanoacrylate; SOV, superior ophthalmic vein; UV, uncal vein; TVE, transvenous embolization

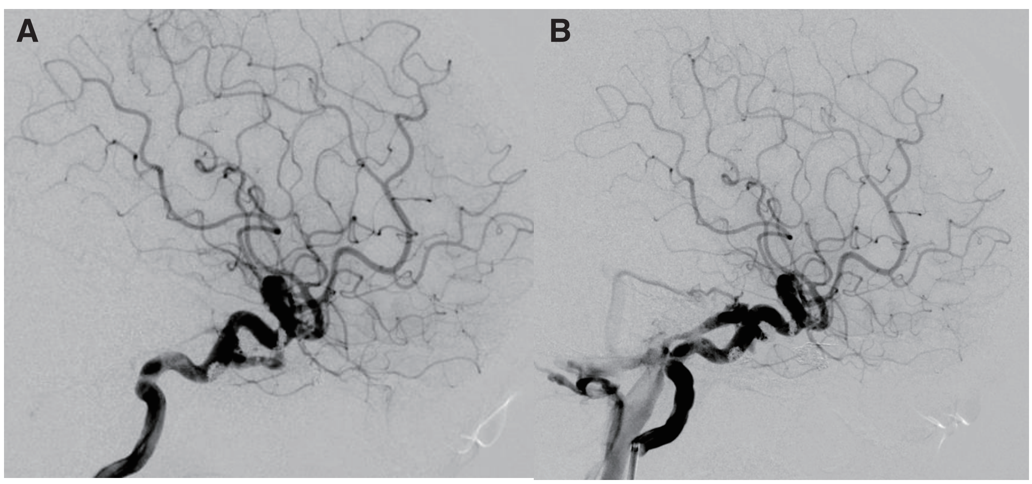

Fig. 3 Comparative DSA imaging of TVE procedures. (**A**) Postoperative DSA following the first TVE shows complete disappearance of intracranial venous reflux, with observed slow flow in the right CS and IPS. (**B**) Preoperative DSA for the second TVE reveals an increased flow in the shunt and reflux extending to the transverse pontine vein and the contralateral SPS. CS, cavernous sinus; IPS, inferior petrosal sinus; SPS, superior petrosal sinus; TVE, transvenous embolization

post-procedure, the right eye pain resolved, ocular symptoms improved, and a decrease in abducens nerve palsy was noted starting the following day.

Regrettably, around 1 month after the operation, the right abducens nerve palsy returned. Compared to the DSA image taken after the first treatment, the BV had enlarged, and the coil mass appeared more compacted within the aneurysm (**Figs. 3B** and **4A**). In the second treatment, considering the possibility of balloon-assisted coil embolization at the shunt point from the arterial side, a 6-Fr sheath was punctured under ultrasound guidance, and a a 6-Fr Envoy guiding catheter (Codman Neuro, Raynham, MA, USA) was placed in the right ICA. On the venous side, as in the first surgery, an 8-Fr Roadmaster was guided into the right IJV from femoral vein, the TACTICS catheter was advanced into the cavernous sinus, and the Headway 17 was used to select the refluxing venous vessel. As a result, 1 coil and 20% NBCA were used to occlude the BV (**Fig. 4A**–**4C**). To avoid any deviation toward the ICA while inserting the coil into the aneurysm, a neck plasty was carried out using the Scepter XC (Terumo), and 3 more coils were added (**Fig. 4D**). The procedure was completed, and total shunt occlusion was achieved through internal carotid arteriography (**Fig. 4E**).

After the surgery, the right eye exhibited reduced conjunctival congestion along with improvement in abducens nerve palsy. The patient was discharged 1 week post-operation. Two years post-operation, the patient continues symptom-free. MRA images taken 2 years after the procedure also revealed no signs of recurrence.

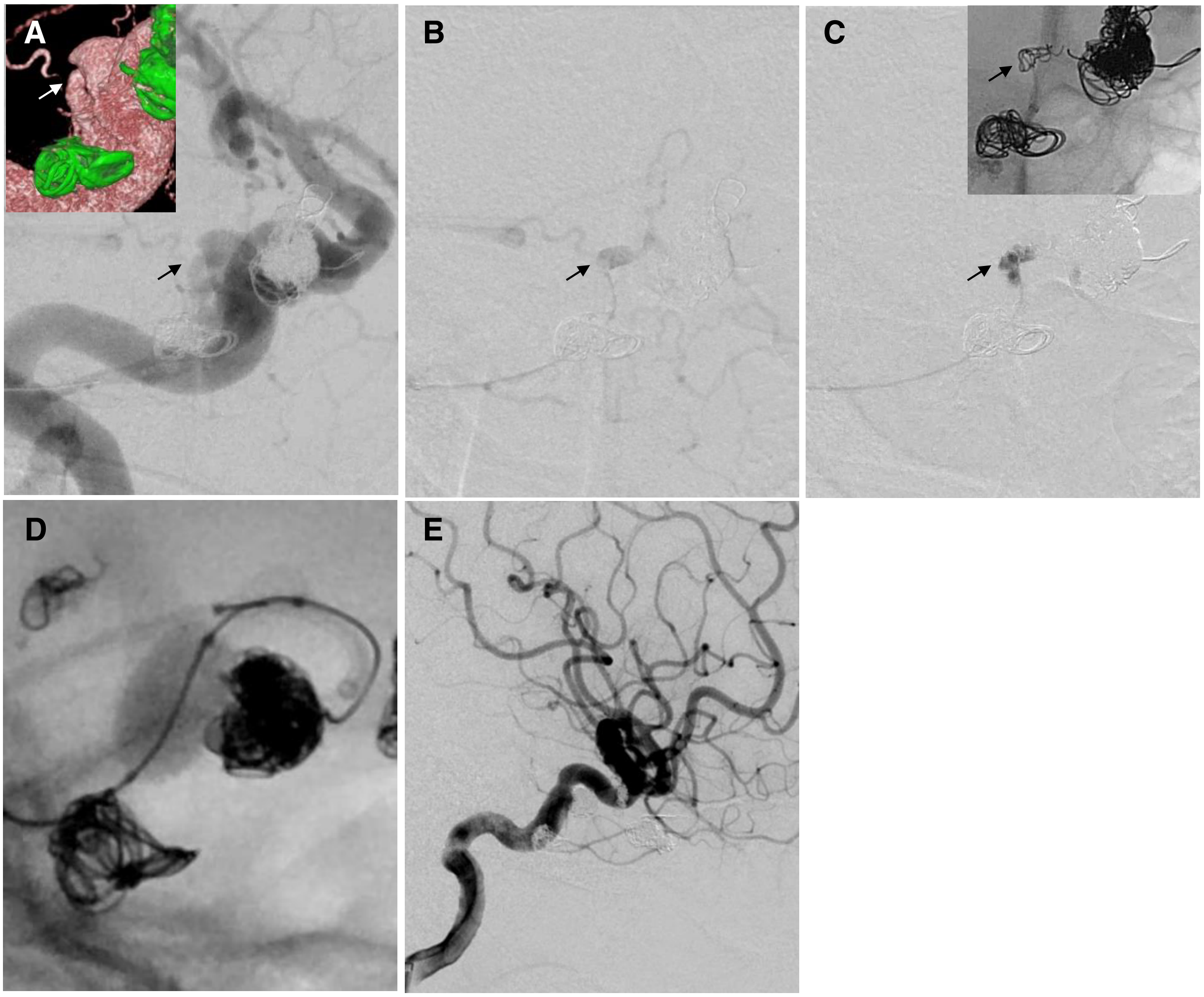

Fig. 4 Intraoperative imaging and intervention during the second TVE. (**A**) DSA of the right CCF showing antegrade flow in the IPS, retrograde flow in the BV (arrow), including transverse pontine vein, and the contralateral SPS. The angiographic images were acquired at right anterior oblique 42° (RAO 33°) and caudal 33° (CAU 40°) projections. (**B**) Micro-DSA of the prepontine BV indicating retrograde flow in the transverse pontine vein and the contralateral SPS (RAO 33°/CAU 40°). (**C**) Embolization of the prepontine bridging vein using coils and 20% NBCA (RAO 33°/CAU 40°). (**D**) Additional coil embolization of the aneurysm via a venous approach and balloon assistance through an arterial approach. (**E**) Complete resolution of shunt flow was observed following the second TVE. BV, bridging vein; CCF, carotid-cavernous fistula; IPS, inferior petrosal sinus; NBCA, *n*-butyl-2-cyanoacrylate; SPS, superior petrosal sinus; TVE, transvenous embolization

The use of NBCA was approved by the Off-Label Use Committee of our hospital. This study was approved by the Institutional Review Board of Nagoya University Hospital (2020-0257).

Discussion

This report discusses a case of CCF linked to EDS in a patient who underwent TVE by combined use of coils and NBCA. During the first treatment, a significant reduction in shunt flow was achieved; however, due to the patient's underlying vascular fragility, natural occlusion did not occur, and a rapid increase in shunt flow was observed within a short period. However, this increase in shunt volume clarified the origin of the bridging veins, enabling us to perform appropriate second treatment. Consequently, we achieved long-term complete occlusion after just 2 treatment sessions. Given the high success rate of endovascular embolization through the transvenous approach, it is frequently chosen as the initial treatment option, and coils are reported as embolization material.[4,5] We have employed coils and NBCA as TVE embolic agents. However, no reports have been published regarding their efficacy. This approach has several advantages. By reducing the number of coils used, the visibility of the cavernous sinus and refluxing veins can be preserved until the final stages of embolization, enabling safe and complete occlusion. Also, compared to coil-only treatment, this method is more cost-effective. In addition, although several complications related to punctures have been documented in endovascular treatment for EDS,[6] this case achieved 2 successive procedures without complications through direct puncture and compression hemostasis. When performing endovascular treatment, it is essential to consider the presence of EDS and employ gentle techniques to ensure safe and effective treatment.

EDS is an autosomal dominant connective tissue disorder characterized by collagen synthesis abnormalities, leading to joint hypermobility, skin hyperextensibility, and tissue fragility. EDS is categorized into 13 subtypes. The estimated prevalence across all subtypes is approximately 1 in 150000 individuals. Our case presentation closely mirrored the characteristics of vascular EDS (vEDS), supported by a history of juvenile vascular ruptures (a ruptured left posterior tibial artery aneurysm) and CCFs, alongside features typical of classical EDS. Clinically, vEDS is marked by delicate, translucent skin that easily bruises and the fragility of internal organs, including the intestines and uterus. The condition is also associated with vascular vulnerability, resulting in an elevated risk of aneurysms and arterial ruptures. Arterial complications occur frequently in vEDS, with arterial dissection and rupture reported in 65% of patients. Complications in childhood are uncommon; 25% of cases are first detected by age 20, with over 80% experiencing 1 or more complications by age 40. EDS carries a bleak prognosis, as 80% of those affected face vascular issues or organ rupture by age 40, and their median lifespan is only 48 years. CCF occurs in 2.4%–9.8% of cases, with half resulting in aneurysm rupture.[7,8] The primary cause of EDS is mutations in the COL3A1 gene, which encodes type III procollagen chains, an essential protein in the wall structure of blood vessels and hollow organs.[9,10] The definitive diagnosis of vEDS is confirmed through the detection of pathogenic mutations in the COL3A1 gene along with other pertinent genes. Although our case satisfied the clinical criteria for an EDS diagnosis and the clinical findings strongly suggested vEDS, a conclusive diagnosis of vEDS could not be made because the patient opted out of genetic testing.

TVE by combination of coils and NBCA enabled precise embolization of the refluxing veins and allowed for a neat arrangement of coils. During CCF embolization procedures, the shunt flow tends to be quite significant. As a result, selectively embolizing only the shunt point may lead to incomplete occlusion. Therefore, it is advisable to embolize the entire CS, encompassing the refluxing veins. However, in the final stages of embolization using only coil, the previously deployed coils may reduce visibility, potentially making it difficult to select target-specific refluxing veins from the CS. This is a risk that reflux veins may persist after cavernous sinus packing. Additionally, this could potentially exacerbate the issue due to mass effect and the accumulation of multiple coils within the CS.[11] From a long-term perspective, vascular fragility leads to many recurrences despite the shunt seeming completely occluded, and retreatment poses challenges due to the excessive coils obstructing optimal visibility. Our method minimized the number of coils utilized while ensuring visibility, allowing for selective occlusion of reflux veins and fistula. The visibility achieved was consistent in the second procedure. There are several important tips for this treatment method. First, since the microcatheter is removed after NBCA injection for each reflux vein, it is necessary to reintroduce a new microcatheter. To shorten the procedure time and reduce the risk of difficulties in catheter navigation, it is crucial to navigate small-bore, highly flexible distal access catheter, such as the TACTICS catheter, to the CS and maintain the access route. Second, as the embolization progresses, visibility decreases, making it essential to preemptively identify reflux veins that may be challenging to navigate and plan the embolization sequence accordingly. If ensuring visibility is deemed difficult, an alternative approach is to use a double-catheter setup, where 1 catheter is pre-positioned in a reflux vein expected to be difficult to access. In such cases, selecting an 8-Fr guiding catheter for venous approach is advantageous, as it allows for the addition of an extra microcatheter during the procedure. One of the drawbacks of this method is the potential risk of neurological symptoms due to NBCA-induced inflammation. The use of coils in combination with NBCA helps prevent the widespread dispersion of NBCA, thereby contributing to the risk reduction. It is also important to stop NBCA injection before significant reflux into the cavernous sinus occurs when the selected reflux vein appears to be occluded.

Regarding the treatment methods and puncture site, despite reports of elevated morbidity and mortality associated with endovascular procedures for treating CCF, many studies advocate for endovascular embolization over traditional surgical methods due to the fragility of the vasculature. Recently, Adham et al. published a case series involving 13 patients with CCF caused by vEDS, all of whom underwent successful treatment with no perioperative or in-hospital complications.[8] Hence, patients with EDS can be managed safely with careful monitoring for potential complications in those at high risk. A venous approach is preferred due to frequent reports of hemorrhagic complications at the arterial puncture site. The transvenous approach limits the risk of ectopic injury because veins have lower pressure than arteries, and it allows for a reduced puncture profile for arteries. Even complications at the puncture site, which accounted for a significant proportion of morbidity in past reports, indicate that recent findings show a combined skin incision with direct puncture or a cutdown of the artery can reduce hemorrhagic complications at the access site by allowing direct visualization during vascular manipulation.[11–14] In our case, we reduced the arterial puncture profile while allowing an increased profile on the venous side, employing an 8-Fr puncture for TVE. Consequently, there were no complications during the ultrasound-guided punctures and compression hemostasis following 2 treatments.

Hemorrhagic occurrences in distant vessels, such as the splenic and iliac arteries, have been noted in 22%–35% of individuals with vEDS,[1,2,15] possibly due to a decrease in the intima and media vessel thickness, which increases circumferential wall stress.[16] Thus, transarterial maneuvers should be minimized. Therefore, surgeons ought to adopt an approach that integrates TVE with transcatheter arterial embolization (TAE) when performing TVE alone proves challenging. In our case, on the arterial side, we employed balloon assistance to maintain flow control and prevent coil migration while maximizing coil density, all while aiming to minimize catheter manipulation. At the conclusion of the initial surgery, a slight residual shunt was noted. Although further TAE or complete embolization of the CS was considered, the lack of intracranial reflux, concerns about complications from adding TAE in EDS cases that carry high complication rates, and the need to maintain visibility for possible retreatment led us to favor close patient monitoring during regular follow-up visits. In the end, the patient's symptoms showed immediate improvement following the first surgery; however, these symptoms later deteriorated due to the fragility of the vascular wall. It is thought that achieving natural occlusion remains challenging, even with reduced shunt volume. Furthermore, the increase in shunt volume noted in our case highlighted the outflow route to the bridging veins, thus aiding in the necessary additional treatment. The combination of coils and NBCA during the second embolization improved visibility, making this technique highly recommended.

Conclusion

We successfully handled a case of CCF linked to EDS by combined use of coils and NBCA. The use of coils combined with NBCA enabled stepwise embolization while preserving visibility, demonstrating its effectiveness.

By remaining clinically vigilant regarding the underlying EDS and distributing devices across the arterial and venous sides of the CS to reduce the chance of arterial puncture, we were able to perform endovascular treatment safely, even with direct puncture.

Disclosure Statement

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