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Spontaneous Regression of an Unruptured Arteriovenous Malformation Due to Drainer Vein Thrombosis in a Patient with Protein S Deficiency: A Case Report and Literature Review

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Abstract

Spontaneous regression of an arteriovenous malformation (AVM) is a rare condition observed in 0.3%-1.3% of patients with AVMs and is most likely caused by hemorrhagic events. The regression of an unruptured AVM is rarer than that of a ruptured AVM. Moreover, due to its low frequency of occurrence, the etiology and natural course of spontaneous regression of an AVM is still unclear. This is the first report presenting a case of a spontaneous regression of an unruptured AVM caused by a gradual drainer vein thrombosis that was suspected to result from hypercoagulability due to protein S deficiency.

Keywords: spontaneous regression, unruptured arteriovenous malformation, drainer thrombosis, protein S deficiency

Introduction

Spontaneous regression of an arteriovenous malformation (AVM) is extremely rare and is observed in cases of untreated AVM during follow-up. Spontaneous regression of AVM is reported in 0.1%-1.3% of patients,[1)] with most of the nidus obliterations caused by AVM rupture. Thus, the mechanism of the spontaneous regression of an unruptured AVM is not well understood. In this report, we present a case of a spontaneous regression of an AVM caused by thrombosis of the draining vein, explained by a hypercoagulable status due to protein S deficiency. We were able to elucidate its clinical course and etiology by analyzing long-term magnetic resonance imaging (MRI) follow-up data.

Case Report

A 33-year-old woman was referred to our department for gamma knife radiosurgery. She had no history of pregnancies, a medical history of oral contraceptive consumption, or a family history of thromboembolic disease. She was diagnosed with an unruptured AVM following an MRI performed to identify the cause of her loss of consciousness. Digital subtraction angiography revealed an AVM on the fronto-parietal lobe with a nidus size of 43 mm on both internal carotid and vertebral angiograms. The feeding arteries were the right pericallosal artery, right posterior pericallosal artery, and angular artery, and the draining veins were the great vein of Galen and the cortical vein draining into the superior sagittal sinus, both tortuous with no sign of stenosis. A flow-related aneurysm was located at the bifurcation of the right pericallosal artery (Fig. 1). Due to the large size of the AVM, staged gamma knife radiosurgery was proposed to the patient, but she did not accept the treatment plan and preferred observational MRI follow-up. The patient underwent 15 follow-up MRI procedures in the next seven years and had no symptoms, occurrences of seizures, or radiological findings of AVM rupture. However, she refused to undergo angiography until she was transferred to our department after her second epileptic seizure.

One year after the first MRI, a follow-up MRI revealed perifocal edema of the nidus with an intravenous throm-

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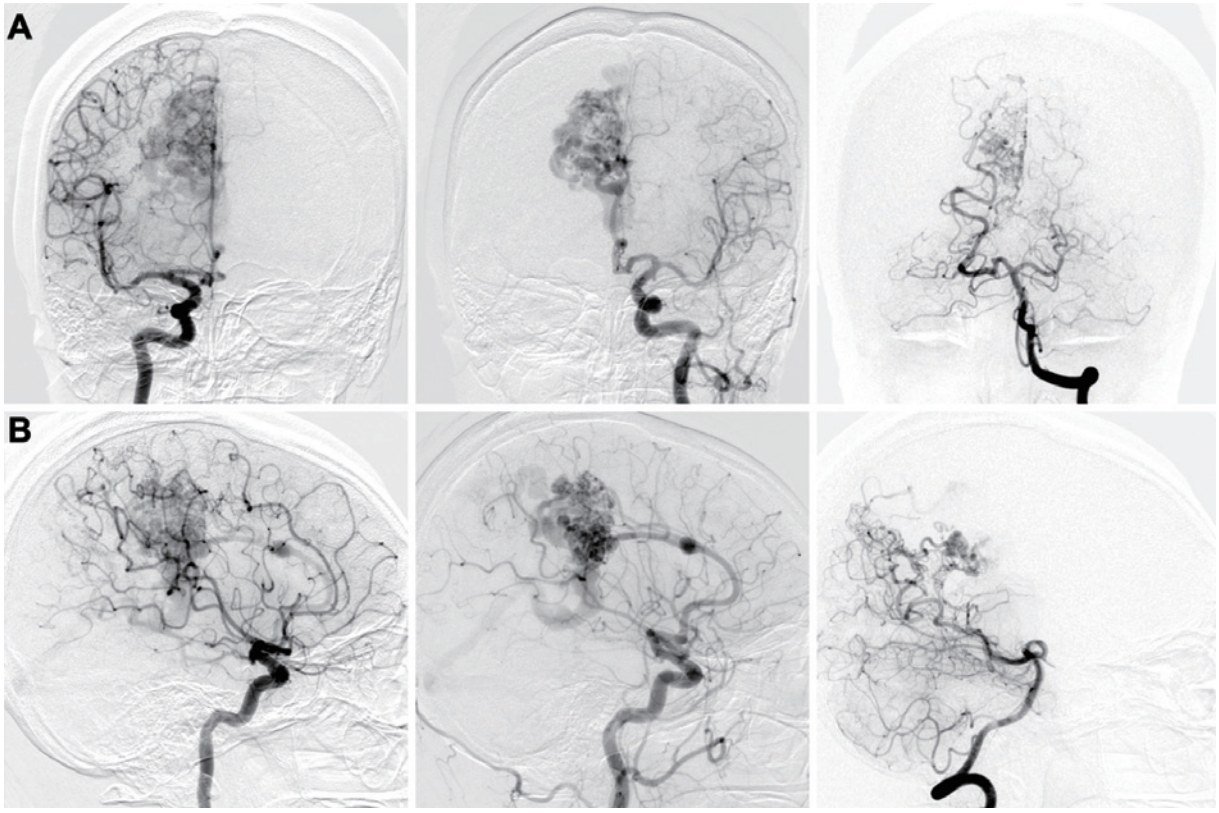

Fig. 1 Initial cerebral angiography (right internal cervical artery, left internal cervical artery, and left vertebral artery). A) Frontal view. B) Lateral view. A large arteriovenous malformation with a 43-mm nidus, fed by the right pericallosal artery, right posterior pericallosal artery, and angular artery, is seen in the right fronto-parietal lobe. The draining veins are the great vein of Galen and the cortical vein draining into the superior sagittal sinus. A flow-related aneurysm is seen at the bifurcation of the right pericallosal artery.

bosis of the draining vein. The feeding artery, which is the enlarged anterior cerebral artery, and the dilated vein of Galen showed reduced diameters. Three years later, signs of another thrombosis were detected with increased brain edema. The nidus, feeding artery, and draining vein also showed a regression in size. Five years later, MRI revealed signs of an additional thrombotic event without an increase in brain edema. At this time, the feeding artery and draining vein had normalized in size. Eight years after the initial presentation, the patient developed an epileptic seizure and was admitted to our department, and we found that her MRI revealed signs of another thrombotic event (Fig. 2). The right internal carotid angiogram and both vertebral angiograms revealed complete obliteration of the AVM, while the left internal carotid angiogram showed a small residual nidus in the capillary and venous phases and a decrease in the size of the flow-related aneurysm (Fig. 3). MRI images revealed the gradual occlusion of the AVM caused by thrombotic events in the draining vein, resulting in near-complete nidus obliteration.

Evaluation for the hypercoagulable state revealed protein S deficiency (protein S activity 40.0%, protein S total antigen 84.0%, and protein S free antigen 65.0%), and additional work-up for deep venous thromboses revealed negative results on echosonography. Considering the small residual lesion observed on the angiogram, we refrained from using anticoagulants to avoid recanalization and rupture of the AVM.

Discussion

Spontaneous regression of an AVM is an extremely rare pathology observed in cases of untreated AVM during follow-up. These lesions tend to be small, with a single superficial draining vein.[2] In the present case, the patient had a large nidus with few arterial feeders and two draining veins, including a deep drainer. However, several studies have reported that most of the nidus obliterations tend to be caused by the rupture of the AVM. The mass effect of the hemorrhage causes hemodynamic changes, which result in a reduction of blood flow, and gliosis resulting from the hemorrhagic event causes the venous drainage to taper. However, information on the incidence and cause of obliteration is limited. In a case series of 27 spontaneous obliterations reported by Patel et al., only three (11%) were unruptured cases.[3] In a study by Liew et al., no unrup-

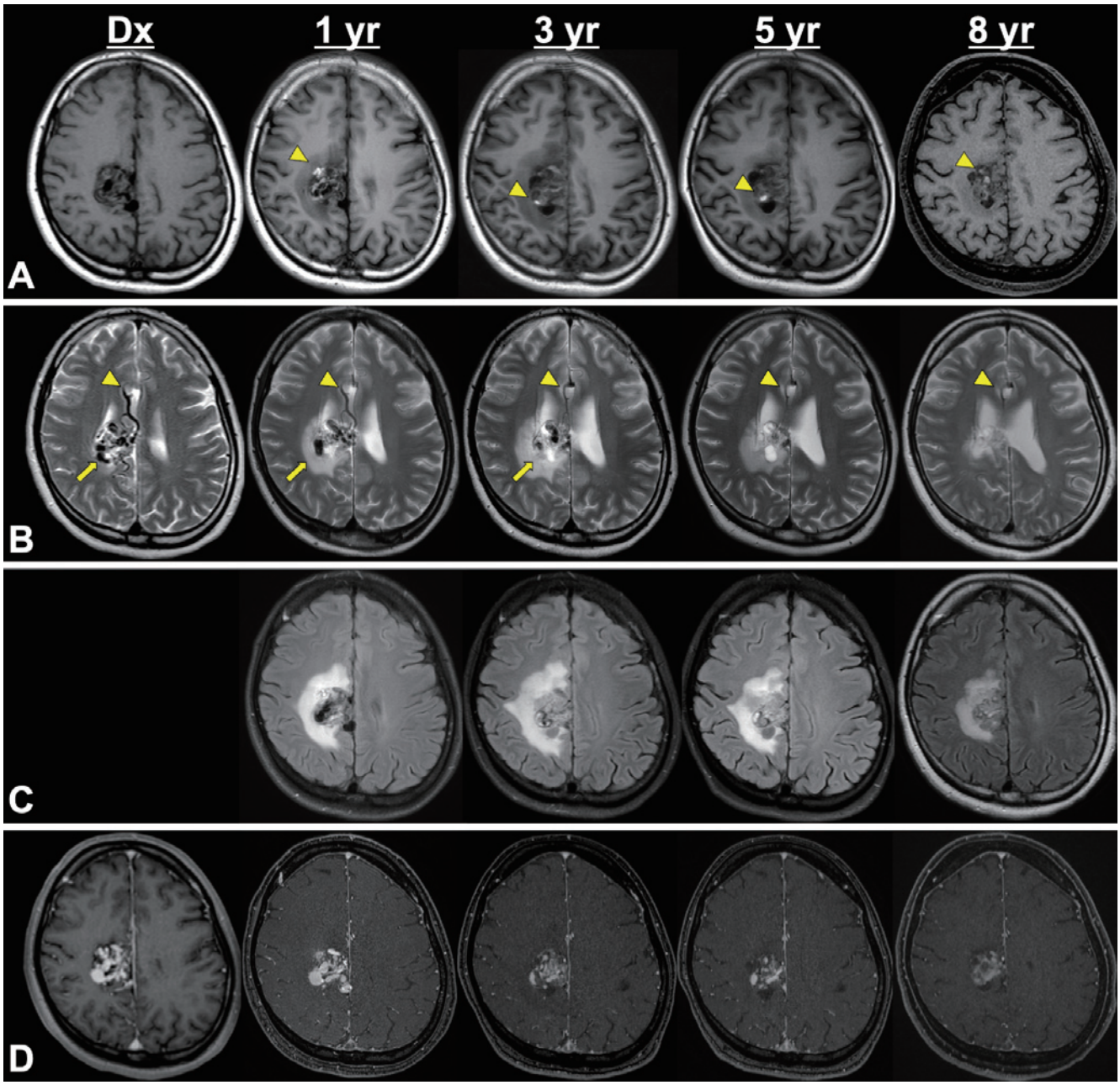

Fig. 2 Follow-up magnetic resonance imaging during eight years.
A) Axial unenhanced T1-weighted images. Signs of thrombosis are seen on each image (arrowheads). B) Axial T2-weighted images. The enlarged anterior cerebral artery as the feeding artery (arrowheads) and the draining vein (arrows) showed gradual normalization in size. C) Axial fluid-attenuated inversion recovery images. Brain edema was first detected on the magnetic resonance imaging performed one year later and showed gradual remission over seven years. D) Axial contrast-enhanced T1 or magnetic resonance angiographic images. A gradual decrease in the size of the contrast-enhanced lesion is seen.
Dx; Diagnosis, yr; years from diagnosis

tured spontaneous obliteration cases were reported in a group of 154 cases of untreated AVM.[1] In a long-term, single-institute study, among 3,573 cases of AVM, only one case of spontaneous obliteration of an unruptured AVM was detected.[4] A literature review on the spontaneous regression of AVM by Kritikos et al. revealed that 30% of the patients had no history of hemorrhage.[2] Accordingly, the true incidence rate of spontaneous regression of an unruptured AVM is unclear.

Several hypotheses have been proposed to explain the mechanisms, classified as mechanical and hematological, of the spontaneous regression of AVMs.[5,6] The mass effect

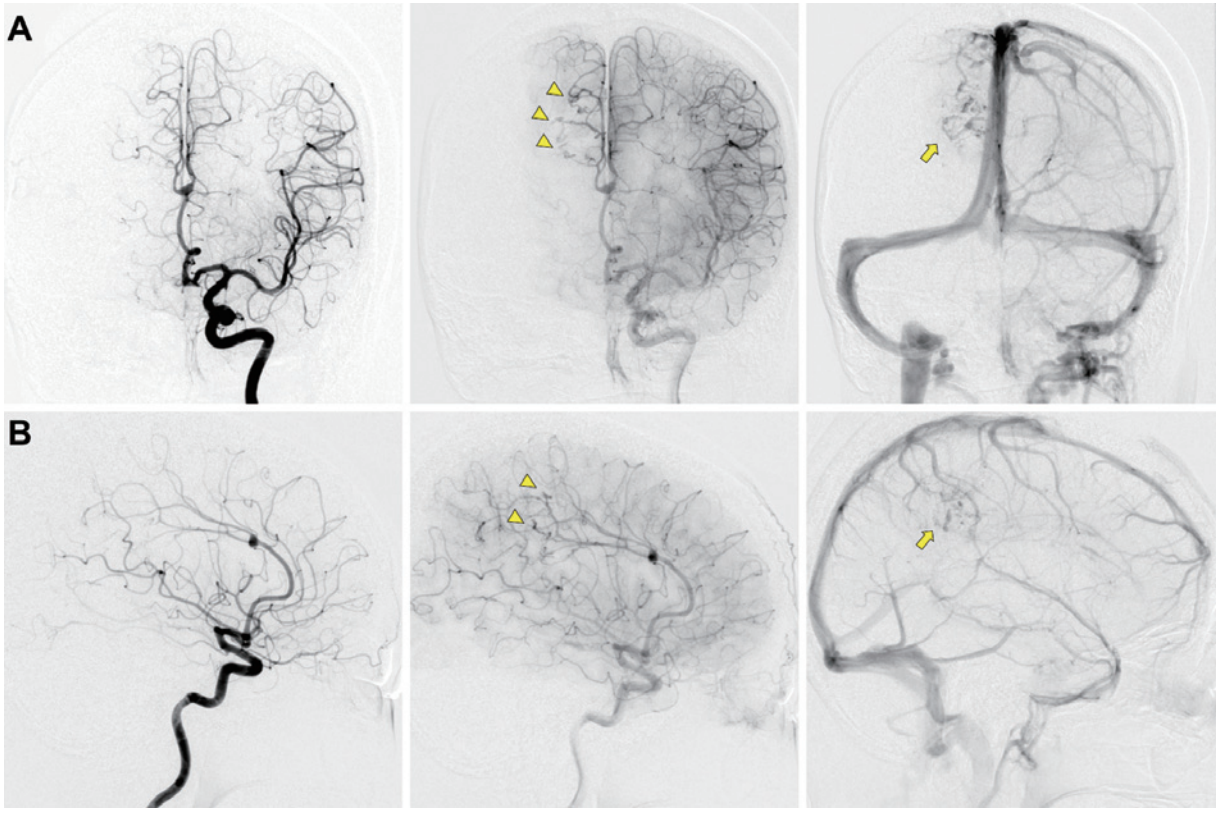

Fig. 3 Second cerebral angiography performed eight years later.
A) Frontal view. B) Lateral view.
Left internal cervical angiogram in chronological sequence (arterial phase, capillary phase, and venous phase). Complete obliteration of the nidus is observed in the arterial phase. Flow-related aneurysm shows a decrease in size. A slight residual component is observed in the capillary phase (arrowheads). Pooling of the contrast agent is observed in the venous phase (arrows).

of hemorrhage or edema, occlusion of the feeder or drainer due to arteriosclerosis, and thromboembolisms are considered mechanical factors. Hypercoagulative states caused by certain medical conditions,[7,8] congenital diseases,[9,10] pregnancy,[4,11] and oral contraceptive use[12] are proposed as hematological causes; however, only a few studies could confirm these causes. Link et al. reported that hypercoagulability caused by the Leiden factor V mutation induces regression of AVM.[9] In the present case, the patient had a history of bleeding from the AVM, which could also have caused the regression. Furthermore, the present case showed only a partial regression of the AVM, and the remaining nidus was treated by embolization and surgical resection. Taha et al. reported a case of acute thrombosis caused by a rare heterozygous prothrombin gene mutation.[10] Due to severe venous infarction, the patient in their study died in the acute phase of the disease. Since this was an autopsy-proven case of spontaneous regression, there were no angiographic images of the AVM and its regression. Arenas-Ruiz et al. were able to demonstrate the cause of spontaneous regression of an unruptured AVM as a multiple myelosis-induced prothrombic state. Angiography revealed the complete disappearance of the AVM.[7] However, they were not able to capture the thrombosed vein on the radiological image, and the follow-up period was not long enough to ascertain the long-term prognosis of the condition. In the present case, we could illustrate the gradual thrombotic events using MRI and elucidate the cause and long-term medical course.

Hereditary protein S deficiency is a rare pathological condition, with the incidence rate reported to be 0.03%-0.13% in a study of 3,788 healthy Scottish blood donors.[13] In the Japanese population, the estimated prevalence rate is reported to be 1.12%.[14] It is a well-known risk factor for cerebral venous thrombosis;[15] thus, in the present case, protein S deficiency could have contributed to AVM regression by causing thrombosis of the draining vein. When thrombophilia is considered to have caused a thrombotic episode, anticoagulants are initiated as prophylaxis. In the present case, we avoided anticoagulant therapy due to concerns regarding the recanalization of the AVM. Therefore, the patient will be carefully monitored for any thrombotic events.

Recanalization of a spontaneously regressed AVM is one of the events that should be considered during subsequent follow-ups. Only a few cases have been reported,[3,16,17] al-

though the incidence rate is reported to be 6.4%.[1] Furthermore, a case of a ruptured, regressed AVM has been reported.[18] Unlike the present case, the formation of a flow-related aneurysm after AVM occlusion has also been reported.[19] This difference can be explained by the gradual decrease in intra-arterial pressure, which is an important hemodynamic factor in aneurysm formation, through four long-term thrombotic events in the present case. However, these events can lead to further complications. One study reported a case of spontaneous thrombosis of an unruptured AVM followed by an ischemic stroke,[20] and another reported a case of fatal brain edema due to spontaneous thrombosis.[10] Thus, even after spontaneous thrombosis of the AVM, the patients should be closely monitored since the thrombosis is not always followed by good outcomes. In the present case, gradual obstruction by multiple small thromboses could have contributed to the favorable outcome. Because of the rarity of this pathological condition, the causes of these events are still unknown, and further studies can provide more insights. Since these complications occur over a long period of time, patients should not be considered cured and should be followed up.

In conclusion, to the best of our knowledge, the present case is the first reported case of a near-complete regression of a large, unruptured AVM, the cause of which was confirmed by elucidating the thrombotic events with meticulous long-term MRI follow-ups and angiographic assessments.

Abbreviations

AVM: arteriovenous malformation
MRI: magnetic resonance imaging

Informed Consent

Informed consent was obtained from the patient for the publication of images and this case report.

Ethics

The study protocol was approved by the institutional ethics review committee of NTT Medical Center Tokyo (approval number: 22-138).

Conflicts of Interest Disclosure

None.

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