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Flow diverter therapy for immunosuppressant-resistant vertebral artery fusiform aneurysm due to eosinophilic granulomatosis with polyangiitis: illustrative case

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BACKGROUND Eosinophilic granulomatosis with polyangiitis (EGPA) is a systemic small-vessel vasculitis characterized by the presence of asthma and eosinophilia. Because cerebral aneurysm formation induced by EGPA is a rare occurrence, there is no established treatment strategy for this condition.

OBSERVATIONS A 67-year-old female who was diagnosed with idiopathic eosinophilia 3 months ago developed de novo fusiform aneurysms in the left vertebral, left internal carotid, and bilateral superficial temporal arteries, as noted during a regular follow-up examination of a convexity meningioma. Pathological examination of the resected superficial temporal artery revealed eosinophilic granulomas, which led to the diagnosis of EGPA, as well as EGPA-induced aneurysm formation. As the partially thrombosed vertebral artery fusiform aneurysm enlarged, the compression of the medulla oblongata occurred despite intensive immunosuppressive therapy for 1 year. The patient underwent flow diversion therapy administered using the pipeline embolization device, resulting in complete disappearance of the aneurysm.

LESSONS Considering that the entire circumference of the aneurysmal wall is affected by necrotizing vasculitis, flow diverter therapy would be a reasonable and efficient approach for the treatment of EGPA-related aneurysms in cases in which the patient is nonresponsive to immunosuppressants.

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KEYWORDS eosinophilic granulomatosis with polyangiitis; Churg-Strauss syndrome; vasculitis; fusiform aneurysm; flow diverter

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic antineutrophil cytoplasmic antibody-associated vasculitis accompanied by asthma and eosinophilia.[1] It is characterized by eosinophilic necrotizing inflammation involving small-sized vessels. Involvement of the central nervous system in EGPA is relatively rare (17.3%), while cerebrovascular events, such as ischemic lesions and intracranial hemorrhage, are the most common manifestations.[2] Because the formation of cerebral aneurysm caused by EGPA is unusual, the treatment strategy for this rare condition has not been established.

Herein, we report a case of EGPA-related cerebral aneurysm treated successfully with flow diverter therapy, and present some of the characteristics and treatment of EGPA-related cerebral aneurysms with a literature review.

Illustrative Case

A 67-year-old female who had undergone radiographic follow-up of a small left convexity meningioma for 3 years complained of a gradual increase in eosinophil count. She was clinically diagnosed with idiopathic eosinophilia at the Department of Hematology in our hospital and started treatment with oral prednisolone (20 mg/day). Magnetic resonance imaging (MRI) performed 3 months after the initiation of corticosteroid therapy revealed the presence of de novo multiple fusiform aneurysms in the left vertebral artery (VA), left internal carotid artery, and bilateral superficial temporal arteries, which were not observed previously on MRI performed 3 years ago (Fig. 1A and B). Of note, the VA fusiform aneurysm was partially thrombosed, and vessel wall imaging demonstrated circumferential enhancement along the aneurysmal wall, suggesting the existence

ABBREVIATIONS EGPA = eosinophilic granulomatosis with polyangiitis; MRI = magnetic resonance imaging; VA = vertebral artery.

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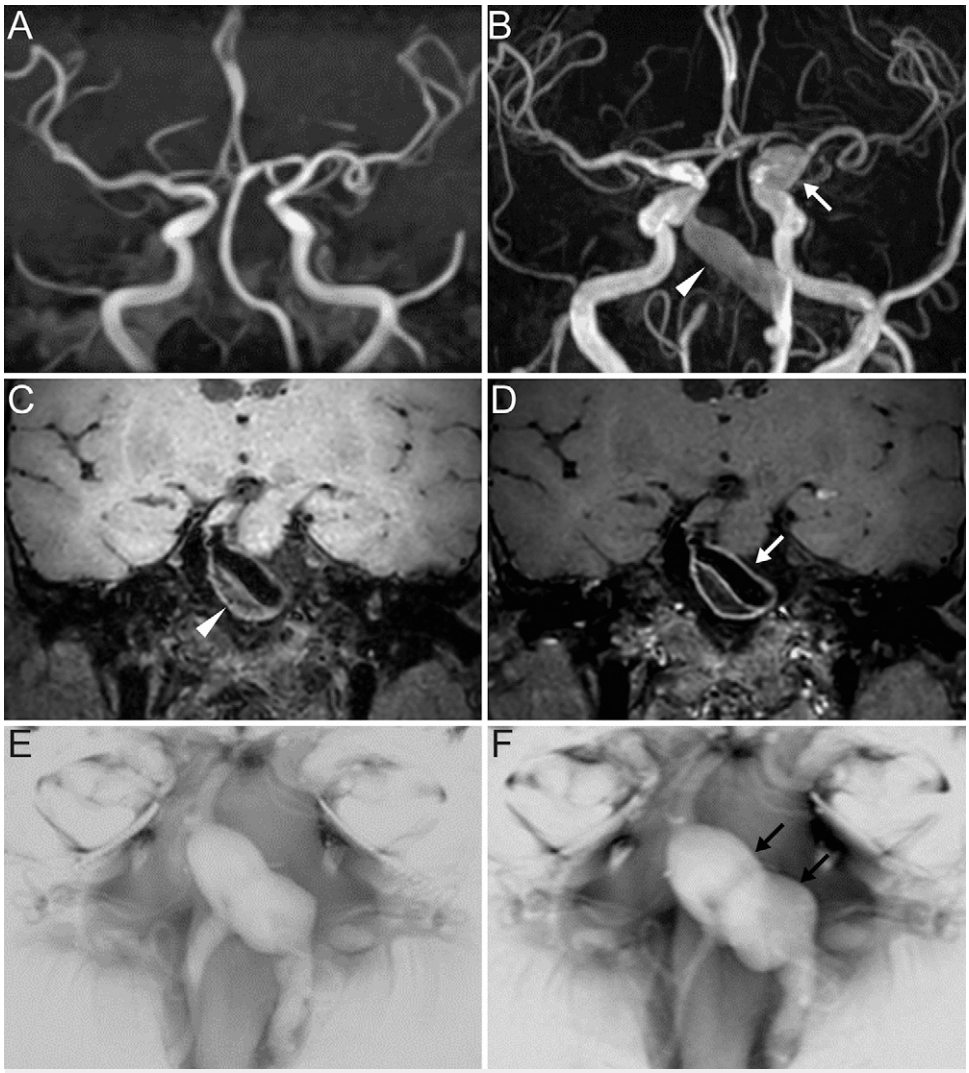

FIG. 1. Magnetic resonance imaging. **A:** Magnetic resonance angiography, 3 years before the diagnosis of EGPA, showing no cerebral aneurysms. **B:** Magnetic resonance angiography, at the time of EGPA manifestation, revealing de novo formation of the left VA (*arrowhead*) and internal carotid artery fusiform aneurysms (*arrow*). **C and D:** Vessel wall imaging before (C) and after (D) contrast injection. Note the partial thrombosis of the aneurysm (C, *arrowhead*) and circumferential enhancement along the aneurysmal wall (D, *arrow*). **E and F:** Basi-parallel anatomical scanning MRI at the time corresponding to (E) and 1 year after EGPA manifestation (F), showing obvious enlargement of the left VA fusiform aneurysm (F, *arrows*).

of active inflammation (Fig. 1C and D). Digital subtraction angiography revealed a left VA fusiform aneurysm extending from the VA union to the left VA (V4 segment) (Fig. 2A). Considering parent artery occlusion or trapping as a choice of treatment for the left VA fusiform aneurysm, the patient underwent balloon test occlusion, which demonstrated no tolerance of left VA permanent occlusion (Fig. 2B). Subsequently, histopathological examination of the resected right superficial temporal artery fusiform aneurysm was performed (Fig. 3A and B). Vasculitis with granulomatous and necrotizing angiitis of the vasa vasorum was observed with an eosinophilic infiltrate (Fig. 3C and D), which led to the diagnosis of EGPA as a cause of eosinophilia, as well EGPA-induced aneurysmal formation. Because these unruptured aneurysms were probably induced by autoimmune vasculitis, a decision was made to provide medical treatment initially, and cyclophosphamide was administered as an adjuvant therapy in addition to prednisolone.

One year after the development of EGPA, follow-up MRI revealed an enlarged left VA fusiform aneurysm causing compression of the medulla oblongata despite intensive immunosuppressive therapy for 1 year (Fig. 1E and F). Based on these findings, we decided to perform reconstructive therapy for the left VA fusiform aneurysm using the pipeline embolization device. The patient received oral antiplatelet drugs (aspirin, 100 mg and clopidogrel, 75 mg) preoperatively and intravenous heparin during the procedure to maintain an activated coagulation time in the range of 250 to 300 seconds. Under general anesthesia, a 5F Navien catheter (Medtronic-Covidien) was navigated to the left VA (V4 segment) via the left brachial artery, and a Marksman microcatheter (Medtronic-Covidien) was introduced into the left posterior cerebral

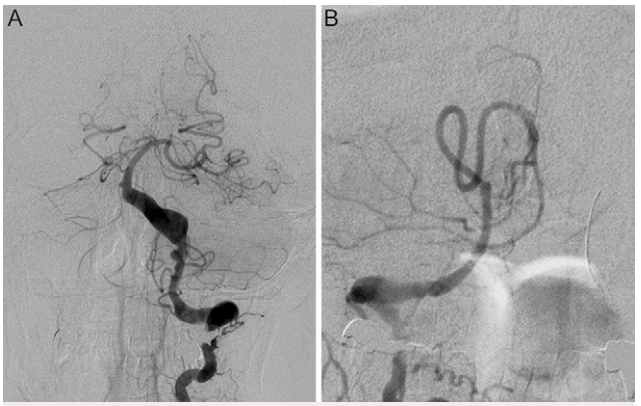

FIG. 2. Digital subtraction angiography at the time of EGPA manifestation. **A:** Left vertebral angiography demonstrating a fusiform aneurysm extending from the union of the VA to the left VA (V4 segment). **B:** Right vertebral angiography under balloon test occlusion of left VA. Note the hypoplastic right VA ending at the posterior inferior cerebellar artery.

artery (P2 segment). Three pipeline embolization devices (Pipeline Flex Shield 3.5 × 35 mm, 3.75 × 30 mm, and 4.0 × 25 mm) were deployed from midbasilar artery to the left VA (V4 segment) to cover the fusiform aneurysm using the telescope technique (Fig. 4A and B). After deployment of the pipeline embolization devices, the flow diversion effect was confirmed. The patient had a favorable postoperative course without neurological deficits and was discharged 7 days after the intervention. Follow-up digital subtraction angiography performed 6 months after the flow diverter therapy revealed complete disappearance of the left VA fusiform aneurysm (Fig. 4C).

Results of the Literature Review

We performed a literature review to elucidate the characteristics of EGPA-related cerebral aneurysms. We searched the relevant literature in Medline database using the following keywords: cerebral aneurysm, eosinophilic granulomatosis with polyangiitis, and/or Churg-Strauss syndrome.

There were six patients with cerebral aneurysms accompanied by EGPA, including the present case, as shown in Table 1.[3–7] The overall mean age of the patients was 44.8 years, and four of six patients (67%) were females. The majority of cerebral aneurysms were fusiform in shape (83%), and the posterior circulation was the most commonly affected (67%). All patients underwent surgery, although the strategies chosen to counteract EGPA-related aneurysms differ on a case-by-case basis.

Discussion

Observations

To date, the characteristics of EGPA-related cerebral aneurysms have not been determined, and to the best of our knowledge, only six cases have been identified, including the present case. According to our literature review, 44.8 years was the mean patient age at the time of aneurysmal detection, including ruptured and unruptured

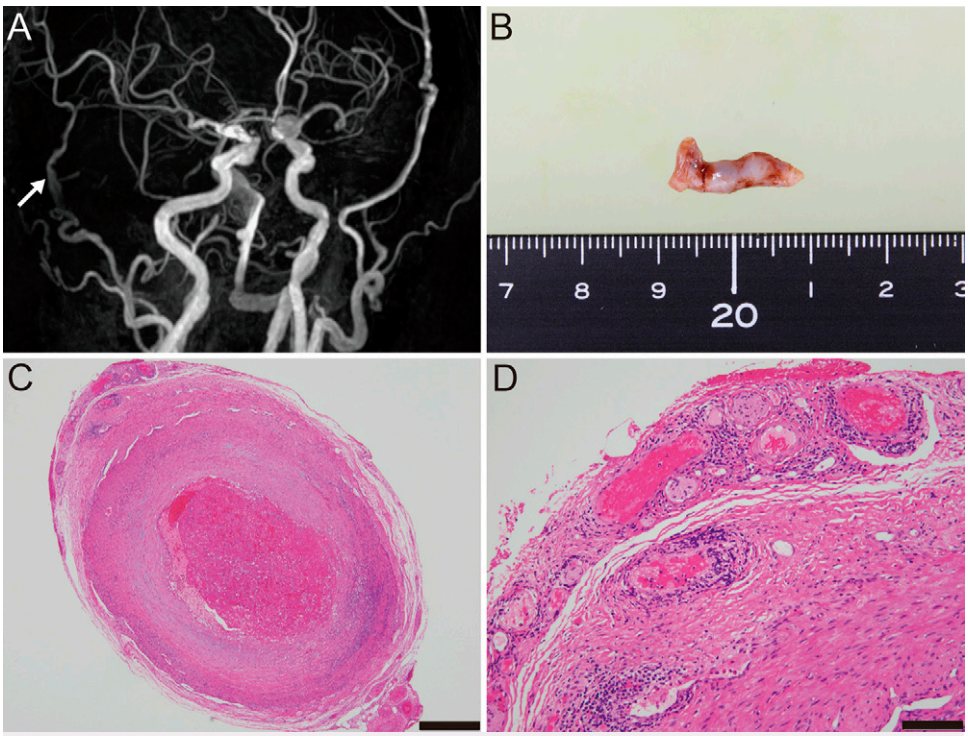

FIG. 3. Biopsy of the superficial temporal artery fusiform aneurysm. **A:** Magnetic resonance angiography, at the time of EGPA manifestation, demonstrating a right superficial temporal artery fusiform aneurysm (*arrow*). **B:** Resected superficial temporal artery fusiform aneurysm. **C and D:** Low-power (C, scale bar: 500 μm) and high-power (D, scale bar: 100 μm) view of histopathological sections revealing vasculitis with granulomatous and necrotizing angiitis of the vasa vasorum. Note the infiltration of eosinophils.

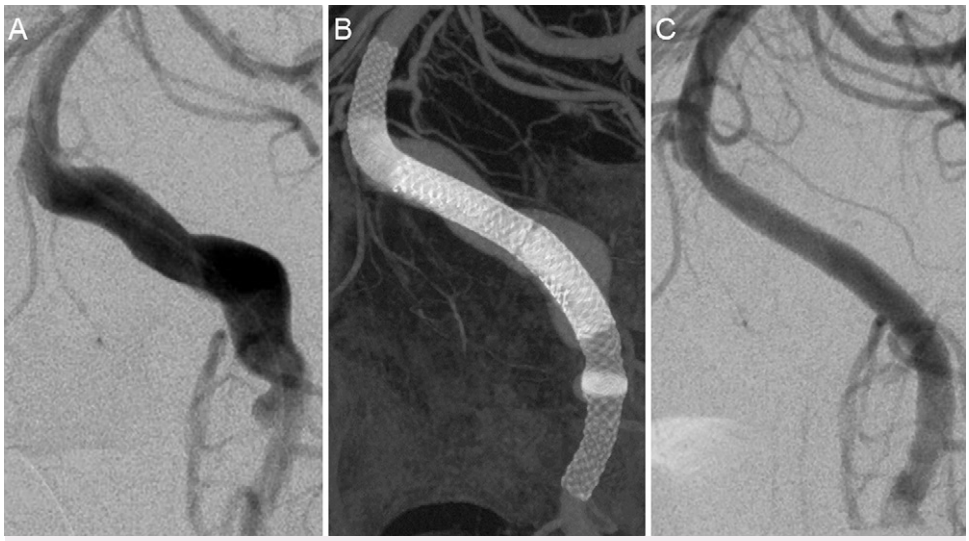

FIG. 4. Digital subtraction angiography during flow diverter therapy (**A and B**) and 6 months after endovascular therapy (**C**). **A and B**: Three pipeline embolization devices deployed from the mid-basilar artery to the left VA (V4 segment) using the telescope technique. **C:** Complete disappearance of the left VA fusiform aneurysm.

aneurysms, which suggests that cerebral aneurysms accompanied by EGPA are more common in younger patients. Most EGPA-related cerebral aneurysms are fusiform and nonsaccular dilatations involving the entire vessel wall for a short distance. EGPA is more likely to induce the formation of fusiform aneurysms; it accounts for 3%–13% of all aneurysms.[8] In addition, the intracranial arteries in the posterior circulation were mainly affected by EGPA. Establishing a diagnosis of EGPA can sometimes be difficult because the syndrome may commonly develop in association with asthma and allergic rhinitis.[1] Indeed, the reported patient could not be diagnosed with EGPA before the biopsy of the superficial temporal artery fusiform aneurysm. Therefore, in cases in which young patients have fusiform aneurysms in the posterior circulation accompanied by eosinophilia, possible involvement of EGPA should be anticipated as an underlying cause of cerebral aneurysms.

The pathogenesis of cerebral aneurysm formation due to EGPA is unknown. Because EGPA is categorized as small-sized vessel necrotizing vasculitis, the involvement of the middle to large vessels, such as the internal carotid artery and VA, is conceptually rare.[1] Large vessel involvement, including the involvement of the aorta, has been reported only in a few cases. Hervier et al.[9] reported that vasa vasoritis, which is the inflammation of small vessels feeding the large arteries, might be involved in the development of large-vessel vasculitis in EGPA, which appears to be similar to Behcet's aortitis involving the media and adventitia. Although this case lacked the histopathological analysis of cerebral aneurysms, histopathological examination of the superficial temporal artery fusiform aneurysm revealed vasculitis with granulomatous and necrotizing angiitis of the vasa vasorum. These findings support the speculation that obliterative vasa vasoritis induces necrosis and thereby weakens the vessel wall of intracranial arteries, leading to the formation of fusiform aneurysms. The involvement of the predisposed posterior circulation could be explained by this hypothesis since the existence of vasa vasorum is more common in the proximal intracranial arteries, such as the vertebral, internal carotid, and basilar arteries.[10] Further studies with pathological specimens of cerebral aneurysms are warranted to clarify the pathogenesis of cerebral aneurysm formation due to EGPA.

Treatment for EGPA-related cerebral aneurysms is not yet established. The cornerstone of medical treatment for EGPA is corticosteroid therapy.[1] Cyclophosphamide can be administered as adjuvant therapy for patients who have substantial vasculitic end organ

TABLE 1. Cases of cerebral aneurysms due to EGPA

Authors & Year	Age/Sex	Aneurysmal Shape	Location	Onset	Surgical Intervention	Outcome
Muraishi et al., 1988[3]	29/F	Fusiform	ACA	Ruptured	Resection	Uneventful
Sakamoto et al., 2005[4]	36/F	Fusiform	VA	Ruptured	Parent artery occlusion	Uneventful
Takekita et al., 2010[5]	34/M	Fusiform	MCA	Unruptured	Clipping	Uneventful
Go et al., 2012[6]	39/M	Fusiform	VA	Ruptured	Stent-assisted coil embolization	Deceased
Menditto et al., 2013[7]	64/F	Saccular	PICA	Ruptured	Coil embolization	Uneventful
Present case	67/F	Fusiform	VA/ICA	Unruptured	Flow diverter therapy	Uneventful

ACA = anterior cerebral artery; ICA = internal carotid artery; MCA = middle cerebral artery; PICA = posterior inferior cerebellar artery; VA = vertebral artery.

damage and are not responsive to corticosteroids. Previous studies have shown the effectiveness of immunosuppressive therapy against EGPA-induced ischemic and hemorrhagic stroke, including spontaneous subarachnoid hemorrhage.[11] Because the cerebral aneurysms in the present case were unruptured and did not require immediate surgical intervention, we decided to perform medical treatment initially. We administered cyclophosphamide in addition to corticosteroids after the development of cerebral aneurysms, which unfortunately resulted in the enlargement of the VA fusiform aneurysm. According to the literature review, surgical interventions range from craniotomy to endovascular therapy. If the effect of EGPA on the aneurysmal wall is localized, surgical clipping or coil embolization may be permissible.[3,7] However, considering the underlying nature of vasculitis, which usually affects the entire circumference of the aneurysmal wall, deconstructive (parent artery occlusion and trapping) or reconstructive therapy (stent-assisted coil embolization and flow diverter therapy) would be a potentially curative treatment. In the present case, balloon test occlusion indicated no tolerance of the left VA occlusion. In addition, because cerebral aneurysms in the present case were unruptured, there was little risk of starting dual antiplatelet therapy preoperatively. Therefore, flow diverter therapy was administered using the pipeline embolization device that resulted in complete obliteration of the aneurysm. Because in-stent thrombosis in the dominant-side VA can be lethal, we chose Pipeline Flex Shield with surface modification that was designed to be less thrombogenic. In addition, because the natural history of EGPA-related cerebral aneurysms is not well known, we are planning to perform annual follow-up of MRI for the patient's lifetime. Taken together, flow diverter therapy would be a reasonable and efficient approach for the treatment of EGPA-related aneurysms in cases in which immunosuppressant therapy is ineffective.

Lessons

Considering that the entire circumference of EGPA-related fusiform aneurysms is affected, deconstructive or reconstructive therapy, including flow diverter therapy, should be considered for the treatment of immunosuppressant-resistant aneurysms depending on the anatomical factors.

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Disclosures

Dr. Ezura reported personal fees from Medtronic outside the submitted work. No other disclosures were reported.

Author Contributions

Conception and design: Sakata, Hayashi, Ezura, Saito. Acquisition of data: Sakata, Hayashi, Saito, Osada. Analysis and interpretation of data: Sakata, Hayashi, Saito. Drafting the article: Sakata, Hayashi. Critically revising the article: Sakata, Hayashi. Reviewed submitted version of manuscript: Sakata, Hayashi, Tominaga. Approved the final version of the manuscript on behalf of all authors: Sakata. Statistical analysis: Hayashi. Administrative/technical/material support: Hayashi, Ezura. Study supervision: Hayashi, Saito, Tominaga.

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