



Intracranial and extracranial multiple arterial dissecting aneurysms in rheumatoid arthritis: A case report

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Abstract

Objective: We describe a case of intracranial and extracranial multiple arterial dissecting aneurysms in rheumatoid arthritis (RA).

Case Presentation: A 29-year-old man with a medical history of RA since 18 years of age was admitted to our hospital for vomiting, dysarthria, and conscious disturbance. At 23, he underwent ligation of the left internal carotid artery (ICA) with superficial temporal artery to middle cerebral artery anastomosis because of acute infarct of the left hemisphere caused by arterial dissection of the left ICA. During the current admission, computed tomography (CT) revealed subarachnoid hemorrhage, and digital subtraction angiography (DSA) demonstrated dissecting aneurysms of the left intracranial vertebral artery (VA) and right extracranial VA. We diagnosed him with a ruptured dissecting aneurysm of the left intracranial VA and performed endovascular parent artery occlusion on the left VA. For the right unruptured VA aneurysm, we performed coil embolization simultaneously. At 2 weeks after the endovascular treatment, follow-up DSA revealed that multiple *de novo* dissecting aneurysms developed on the origin of the left VA and left and right internal thoracic arteries. Those aneurysms were treated with coil embolization. Other remaining aneurysms on the left thyrocervical trunk, right transverse cervical artery, and both common iliac arteries were treated by conservative therapy. While continuing medical treatment for RA, the patient recovered and was discharged to a rehabilitation hospital.

Conclusion: Considering that RA-induced vasculitis can be a potential risk of vascular complications including multiple arterial dissections, physicians should carefully perform endovascular interventional procedures for patients with long-term RA.

Keywords

Intracranial and extracranial multiple arterial dissecting aneurysms, rheumatoid arthritis, *de novo* dissecting aneurysm, endovascular treatment, TNF- α antagonist

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Introduction

Rheumatoid arthritis (RA) is an inflammatory disorder that primarily affects the joints, and in the progressive phase, it can damage systemic organs, including the blood vessels. The systemic inflammation accelerates vascular complications in RA.¹ However, multiple arterial dissections associated with RA are poorly understood. Herein, we describe a rare case of intracranial and extracranial multiple arterial dissecting aneurysms in a patient with long-term RA.

Case presentation

Medical history

A 29-year-old man had a medical history of RA since 18 years of age, and he has been taking methotrexate and prednisolone. His paternal aunt had RA. When he was 23 years old, he developed sudden onset right

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hemiparesis. Magnetic resonance imaging (MRI) and diffusion-weighted imaging demonstrated acute infarct of the watershed area of the left-middle-to-anterior cerebral artery territories (Figure 1(a)). Digital subtraction angiography (DSA) was conducted, and left common carotid artery (CCA) angiography revealed severe stenosis of the origin of the left internal carotid artery (ICA) caused by arterial dissection (Figure 1(b) and (c)). We assumed that the mechanism of the infarct was the hemodynamic stroke or subsequent embolic strokes caused by thrombosis formation due to the arterial dissection. To prevent the recurrence of cerebral infarction, antiplatelet therapy with aspirin was started, and the patient underwent ligation of the origin of the left ICA with superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis. Postoperative DSA confirmed that the ligation of the left ICA was complete (Figure 1(d)), cross flow from the right ICA to the left hemisphere through the anterior communicating artery existed (Figure 1(e)), and STA-MCA anastomosis was patent (Figure 1(f)). He was discharged home with slight right hemiparesis remaining. He continued to take methotrexate and

prednisolone. He started infliximab, a chimeric monoclonal antibody against tumor necrosis factor- α (TNF- α) because of exacerbation of RA, and continued this treatment for 5 years. Two months before the recent emergency hospital admission, infliximab was switched to golimumab, another TNF- α antagonist.

Current admission

When the patient was 29 years of age, he was admitted to the emergency department because of sudden headache, vomiting, and conscious disturbance. Head computed tomography (CT) revealed a subarachnoid hemorrhage (SAH) on the basal cistern and prepontine cistern (Figure 2(a)). His Glasgow Coma Scale score was 13 (eyes, 3; verbal, 4; motor, 6), and the neurological severity of the SAH was determined as Hunt and Kosnik grade 3 and World Federation of Neurosurgical Societies grade III. CT angiography indicated the existence of a dissecting aneurysm of the left vertebral artery (VA). We conducted endovascular embolization with the patient under general anesthesia on the next day of onset. We confirmed that the endovascular access route was intact,

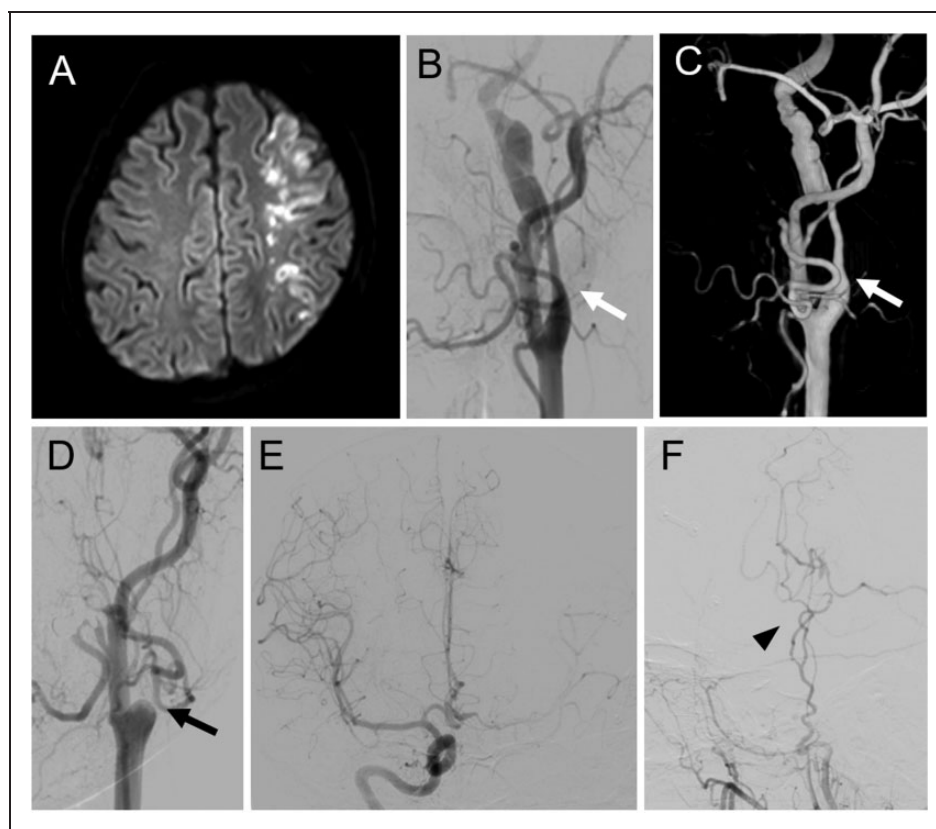


Figure 1. (a) MRI diffusion-weighted image demonstrates acute infarct of the watershed area of the left middle to anterior cerebral artery territories. (b, c) Frontal views of left CCA angiography (b) and 3D angiography (c) reveal severe stenosis of the origin of the left ICA caused by arterial dissection (white arrow). (d, e, f) On postoperative DSA, frontal view of left CCA angiography (d) shows complete ligation of the left ICA (black arrow). (e) Frontal view of right ICA angiography shows the existence of cross flow from the right ICA to the left hemisphere through the anterior communicating artery. (f) Lateral view of the ECA angiography shows patency of the STA-MCA anastomosis (double bypass) (black arrowhead).

MRI: magnetic resonance imaging; CCA: common carotid artery; ICA: internal carotid artery; DSA: digital subtraction angiography; ECA: external carotid artery; STA-MCA: superficial temporal artery to middle cerebral artery.

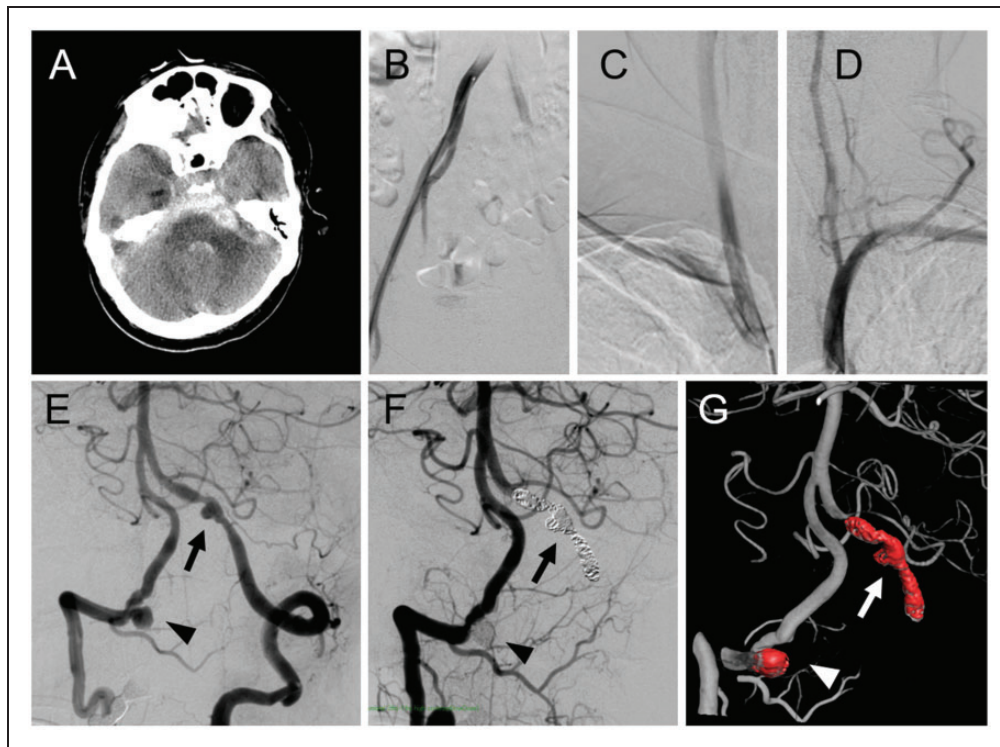


Figure 2. (a) CT image on admission reveals a diffuse SAH on the basal cistern and prepontine cistern, and an especially thick hematoma exists on the left pontocerebellar cistern. (b–d) Pre-treatment DSA shows that the access route is intact, and there is no dissecting aneurysm of both femoral arteries (b), the right carotid artery and right subclavian artery, (c) and left VA and left subclavian artery (d). Although the representative images are relatively faint in (b–d), when the series of images on the angiography are seen, we were able to confirm that there is no aneurysm on the branches. (e) Angiography of both VAs demonstrates a dissecting aneurysm on the left side of the intracranial VA, which is suspected to be a ruptured aneurysm (black arrow), and another dissecting aneurysm of the right extracranial VA (V3–V4 portion), which is suspected to be unruptured (black arrowhead). (f and g) After endovascular treatment, right VA angiography shows that PAO with coil embolization of the left VA dissecting aneurysm (black arrow in f and white arrow in g) and coil embolization of the right VA dissecting aneurysm (black arrowhead in f and white arrowhead in g) are completed. CT: computed tomography; SAH: subarachnoid hemorrhage; DSA: digital subtraction angiography; VA: vertebral artery; PAO: parent artery occlusion.

including both femoral arteries (Figure 2(b)), the right subclavian artery (Figure 2(c)), and left subclavian artery (Figure 2(d)). Angiography of both VAs demonstrated a dissecting aneurysm of the left intracranial VA, which was presumed to be the source of the SAH, and a dissecting aneurysm of the right extracranial VA (V3–V4 portion), which was considered to be unruptured (Figure 2(e)). We diagnosed the patient with SAH due to a ruptured dissecting aneurysm of the left intracranial VA. In order to prevent rehemorrhage, we decided to perform endovascular parent artery occlusion (PAO) with coil embolization of the left VA dissecting aneurysm (Figure 2(f) and (g)). In addition, we treated the unruptured right VA dissecting aneurysm with coil embolization simultaneously (Figure 2(f) and (g)), considering that PAO of the left VA could increase the risk of rupture of the right VA dissecting aneurysm due to the increase in the alternated blood flow stress on the right VA.

At 2 weeks after the first session of endovascular treatment, follow-up DSA revealed multiple *de novo* dissecting aneurysms in the cervicothoracic portion, including on the right internal thoracic artery (RITA)

(Figure 3(a)), proximal part of the left VA, and left internal thoracic artery (LITA) (Figure 3(b)). We performed aortography to confirm the overall image of multiple dissecting aneurysms in the cervicothoracic portion, and aortic dissection was not observed (Figure 3(c)). Considering the risk of aneurysmal rupture, we treated these *de novo* dissecting aneurysms with coil embolization (Figure 3(d) and (e)). When we finished embolization, we noticed that other multiple dissecting aneurysms remained on the origin of the right transverse cervical artery bifurcated from the thyrocervical trunk (Figure 3(d)) and on the origin of the left thyrocervical trunk and costocervical trunk (Figure 3(e)). Immediately before removing the sheath introducer from the left femoral artery, arterial dissections of both common iliac arteries were observed (Figure 3(f)). Those *de novo* aneurysms had not been seen during the initial endovascular treatment (Figure 2(b) to (d)). Because we considered that the damage to the fragile artery due to RA-induced vasculitis during catheterization may be a potential cause of the formation of the multiple dissecting aneurysms, we treated the patient with

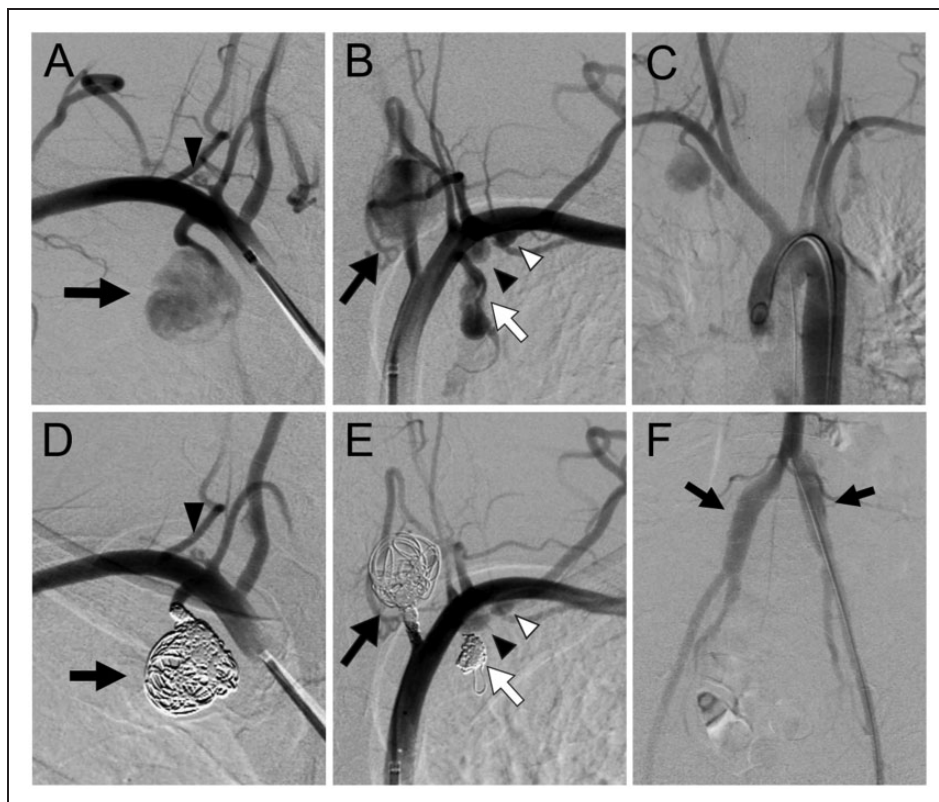


Figure 3. (a–c) Follow-up DSA at 2 weeks after the first session of endovascular treatment reveals multiple de novo dissecting aneurysms in the cervicothoracic portion. (a) Right subclavian artery angiography shows dissecting aneurysms of RITA (black arrow) and the origin of the right transverse cervical artery (black arrowhead). (b) Left subclavian artery angiography shows dissecting aneurysms on the proximal part (V1 portion) of the left VA (black arrow), LITA (white arrow), origin of left thyrocervical trunk (black arrowhead), and costocervical cervical trunk (white arrowhead). (c) Aortography shows an overall image of the arteries and aneurysms in the cervicothoracic portion. (d and e) Complete occlusions with coil embolization of the dissecting aneurysms of RITA (black arrows in d), the left VA (black arrow in e), and LITA (white arrow in e) are confirmed. Other multiple dissecting aneurysms remain on the origin of the right transverse cervical artery (black arrowhead in D), origin of the left thyrocervical trunk (black arrowhead in e), and costocervical cervical trunk (white arrowhead in E). (f) Arterial dissections of both common iliac arteries (black arrows) are revealed by DSA immediately before removing the sheath introducer inserted through the left femoral artery. DSA: digital subtraction angiography; RITA: right internal thoracic artery; VA: vertebral artery; LITA: left internal thoracic artery.

conservative therapy, which included the continuation of medical treatment for RA.

We consulted with staff in the Department of Rheumatology, and reconfirmed the diagnosis of RA based on the findings of polyarthrititis, ulnar drift deformity, radiography, and highly elevated level of the anti-cyclic citrullinated peptide antibody. There were no apparent features of hereditary connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome (EDS). No pathogenic variants were detected through a next-generation sequencing-based custom panel analysis comprising 17 causative genes for hereditary connective tissue disorders (*ADAMTS2*, *B4GALT7*, *CHST14*, *COL1A1*, *COL1A2*, *COL3A1*, *COL5A1*, *COL5A2*, *FBN1*, *FBN2*, *FKBP14*, *PLOD1*, *SLC39A13*, *TGFBR1*, *TGFBR2*, *TNXB*, *ZNF469*) using genomic DNA extracted from peripheral blood and an Ion PGM (Thermo Fisher Scientific, Carlsbad, CA, USA).²

Outcome

The patient recovered within a month after the second endovascular treatment and was discharged to a rehabilitation hospital to continue medical treatment for RA (methotrexate and low-dose prednisolone and golimumab). Five years after the endovascular treatment, the patient's condition was ameliorated with no significant finding of recurrence of vascular complication including arterial dissection, and follow-up CT angiography showed no significant change in the remaining multiple aneurysms (Figure 4(a)) or both common iliac arteries (Figure 4(b)).

Discussion

It has been suggested that patients with RA who have persistently high levels of inflammation are at greater risk of developing cardiovascular diseases and systemic vascular complications.¹ Rheumatoid vasculitis (RV) is an inflammatory disease that affects blood

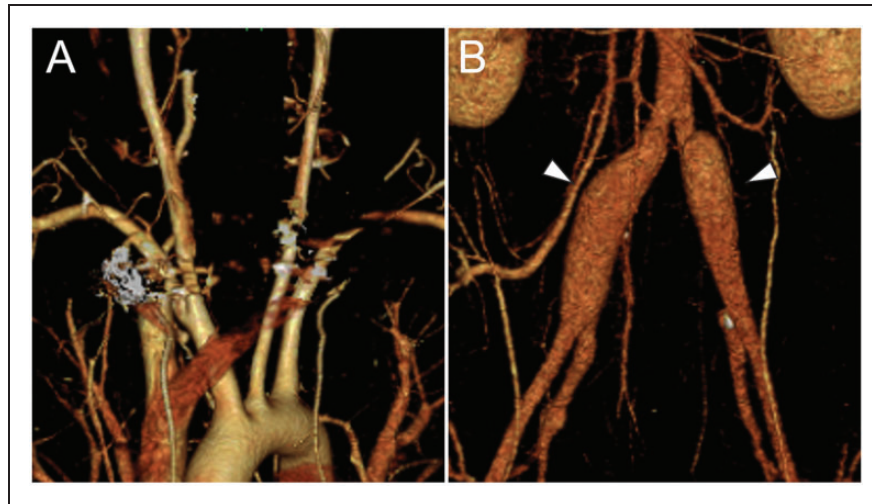


Figure 4. (a and b) Follow-up CT angiography at 5 years after endovascular treatment shows no significant change of the cervicothoracic multiple aneurysms (a) or both common iliac arteries (white arrowheads in b). CT: computed tomography.

vessels directly in patients with RA.³ RV has a heterogeneous clinical presentation that includes skin disorders, neuropathy, eye symptoms, and systemic inflammation.⁴ RV is usually seen in patients with long-standing, severe, seropositive, and often uncontrolled RA. RV typically causes severe injury to the affected blood vessels and most frequently involves small vessels, but it may also involve medium and large vessels.³ With regard to the large vessels affected by RV, rheumatoid aortitis is reported to be a rare feature of severe RA.⁵ As for medium vasculitis, cerebral rheumatoid vasculitis (CRV) has been reported as an infrequent complication in RA, and the characteristic feature of CRV is cerebral parenchymal vasculitis in both cerebral hemispheres.⁶ However, RA-related arterial dissection of large vessels in the intracranial or cervicothoracic part, like in our case, is poorly reported.

The disease activity of RA could be associated with the vascular damage and induce the dissecting aneurysms. We are not able to confirm the patient's previous detailed RA disease activity because he was treated for RA in another hospital before the onset of SAH. The C-reactive protein was 0.77 mg/dL on the current admission due to SAH, and other components of disease activity score such as disease activity score-28 (DAS28), clinical disease activity index (CDAI), or simplified disease activity index (SDAI) were not measured. Since the biological disease modifying anti-rheumatic drugs were switched from infliximab to golimumab for enhancement of RA treatment two months before the onset of SAH, we assume that the disease activity of RA might be high or moderate.

TNF- α inhibitors, such as infliximab or golimumab, have been reported to carry a potential risk of inducing RV, although this idea is still controversial.³ A case report described a rapidly fatal mycotic

aneurysm of the ICA that ruptured in a patient with RA who was taking a TNF- α inhibitor.⁷ In our case, systemic infection, bacteremia, or fungemia was not seen, and it was not assumed that those aneurysms were caused by infection. Moreover, some studies reported that rheumatoid cervical spine disease can cause a VA dissection in patients with RA.^{8,9} In our case, however, findings of cervical spine disease, such as osteophytes, were not seen on radiography. Therefore, we assumed that the state and bioactive condition of RA or RV could affect the formation of multiple arterial dissections and that the medications including the biologics (TNF- α inhibitors) may affect the healing or even deterioration of the multiple dissections.

Except for RA- or RV-related cases, the onset of cervical artery dissections has generally been associated with major head and neck trauma as well as with minor trauma secondary to a wide range of insults. Instead of major trauma, spontaneous cases are considered to be caused by intrinsic factors that weaken the arterial wall, including hereditary connective tissue disorders, infection, hyperhomocysteinemia, migraine, hypertension, fibromuscular dysplasia, atherosclerosis, and low levels of α 1-antitrypsin.¹⁰ Representative hereditary connective tissue disorders exhibiting systemic arterial dissection are Marfan syndrome caused by pathogenic variants in *FBNI*¹¹ and vascular EDS caused by pathogenic variants in *COL3A1*.² The present patient showed no apparent features of hereditary connective tissue disorders, and he was found to have no pathogenic variants in relevant genes through next-generation-based genetic screening. A case of multiple spontaneous cervical artery dissections occurring after ruptured intracranial aneurysm embolization was reported, and the author discussed the effect of head extension during embolization as the prevailing factor in multiple

artery dissections.¹² In our case, the patient's head and neck were not extended during endovascular embolization. In addition, other connective tissue disorders that overlap with RA associated with vasculitis (such as systemic lupus erythematosus, Sjogren syndrome) or tuberculosis have not been diagnosed previously by physical examination and from laboratory findings including autoantibody screening. Because our patient had no other related condition including connective tissue disorders, except for RA, we assume that RV may affect and accelerate the formation of multiple arterial dissecting aneurysms. To evaluate the arterial wall inflammation, the utility of vessel-wall MRI imaging is reported.¹³ We did not perform the vessel-wall MRI imaging on this patient, but it could be useful to better investigate similar cases in future.

In terms of the indication for diagnostic angiography and endovascular treatment, because of the fragile nature of connective tissue, some connective tissue disorders, such as vascular EDS, are often accompanied by neurovascular complications secondary to vessel dissection or aneurysm.¹⁴ In patients with vascular EDS, some articles have reported post-endovascular treatment intracranial hemorrhage¹⁵ or abdominal bleeding¹⁴ due to an unknown cause located at the remote area from puncture or catheterization, i.e., "remote vascular catastrophes." Patients with long-term RA are at greater risk of developing cardiovascular disease,¹ and they occasionally undergo diagnostic angiography and percutaneous coronary intervention for cardiovascular disease, but the arterial dissections after the endovascular procedure are rare. In this case, considering the localization of the *de novo* dissecting aneurysms on the branches of subclavian arteries bilaterally, we assume that during the first procedure the guidewire could have been inserted in the branches. Hence, the guidewire and catheter navigation in the predisposed condition of long-term RA could have induced dissections in those branches two weeks after the endovascular procedure performed bilaterally on the vertebral arteries. Although the risk of arterial dissection may not be so great in patients with RA, considering that RV can induce arterial fragility, RA may be a potential cause of *de novo* multiple dissecting aneurysms after endovascular treatment. Physicians should consider these potential hazards when there is a need to conduct an endovascular procedure in patients who are suspected to have vasculitis due to long-term RA.

Conclusions

We reported a rare case of intracranial and extracranial multiple arterial dissecting aneurysms in RA. When performing endovascular procedures in patients with long-term RA, damage to the fragile

artery during catheterization can be a potential cause of multiple arterial dissecting aneurysms. Thus, physicians should consider the potential vascular risk of RA and carefully perform endovascular procedures in patients with long-term RA.

Declaration of conflicting interests

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