

IgG4-related small-sized occlusive vasculitis in Mikulicz's disease

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ABSTRACT

Mikulicz's disease is one of the IgG4-related diseases (IgG4-RDs) that involves the cardiovascular system; however, small-sized vasculitis is rare in IgG4-related diseases. A 64-year-old man presented with distal occlusive disease and developed left cerebrovascular infarction with occlusion of the middle cerebral artery and diseased temporal artery branches. He underwent superficial temporal artery-middle cerebral artery anastomosis surgery. Histology of the temporal artery biopsy showed smooth muscle cell proliferation with many IgG4-positive plasma cells. He then developed salivary gland inflammation, and Mikulicz's disease was diagnosed. Small-sized occlusive vasculitis was observed in this IgG4-RD. Low-dose corticosteroid therapy is effective in preventing progressive occlusive disease. (*J Vasc Surg Cases and Innovative Techniques* 2019;5:289-92.)

Keywords: Cerebral infarction; Endovascular therapy; IgG4-related disease; Mikulicz's disease; Small-sized vasculitis

IgG4-related disease (IgG4-RD) is a systemic inflammatory disease that can involve the cardiovascular system.¹ It is characterized by fibrosclerosis, lymphocytic infiltration, and IgG4-positive plasma cells.^{2,3} Mikulicz's disease is a known subtype of Sjögren's disease, and recently considered one of the IgG4-RDs associated with salivary and lacrimal gland inflammation.⁴ Vascular involvement in IgG4-RD manifests as large- or medium-sized arterial inflammation, such as periaortitis and coronary arteritis^{1,5,6}; however, small-sized peripheral arteritis is rare.

We report a case of Mikulicz's disease accompanied by systemic small-sized peripheral occlusive disease. The histologic findings of superficial temporal artery biopsy revealed IgG4-related vasculitis. We have obtained the patient's consent to publish his case details and images.

CASE REPORT

The patient was a 64-year-old man with a history of diabetes mellitus, interstitial pneumonia, smoking habit, and repetitive critical upper and lower limb ischemia owing to occlusive disease of multiple small arteries. He presented with digital cyanosis and skin ulcer owing to bilateral occlusion of the ulnar

arteries and superficial palmar arch (*Fig 1, A*). He also developed toe cyanosis and pain owing to bilateral occlusion of the anterior tibial arteries and severe stenosis of the left posterior tibial artery. He stopped smoking at this time. He underwent balloon angioplasty of both the right and left ulnar artery, but revascularization was achieved only in the right ulnar artery. He was treated with aspirin (100 mg/d) and cilostazol (100 mg twice a day). The clinical findings of the upper and lower extremities appeared at different time points, and repeated exacerbation and remission were treated with antiplatelet therapy and a topical skin medication.

Six months after the first balloon angioplasty, he presented to the emergency department with sudden onset of dysphasia (word-finding difficulty). A diagnosis of branch atheromatous disease-type cerebral infarction in the left corona radiata area was made according to brain magnetic resonance imaging findings (*Fig 1, B*). The serum C-reactive protein level was 2.91 mg/dL and white blood cell count was 9500/ μ L (eosinophils, 11.4%). He had a slight fever on admission. Magnetic resonance angiography revealed that the left middle cerebral artery was occluded at the M1 portion (*Fig 1, C*). However, his clinical symptoms were mild and dysphasia disappeared 1 week later.

Single-photon emission computed tomography brain blood flow imaging revealed decreased cerebrovascular reserve in the left middle cerebral artery area compatible with Powers' classification stage 2.⁷ Computed tomography angiography and catheter angiography demonstrated mild stenotic lesion in the parietal branch of the superficial temporal artery preoperatively (*Fig 1, D*); however, we considered that the parietal branch could be used as a donor artery. Angiography was also performed to evaluate the collateral flow from the leptomeningeal anastomosis in the left middle cerebral artery area, which revealed modest collateral flow from the anterior and posterior cerebral arteries despite the decreased cerebrovascular reserve. He subsequently underwent superficial temporal artery (frontal branch only)-middle cerebral artery (M4 portion) bypass surgery. The cross-section of the parietal branch was found to be unusual

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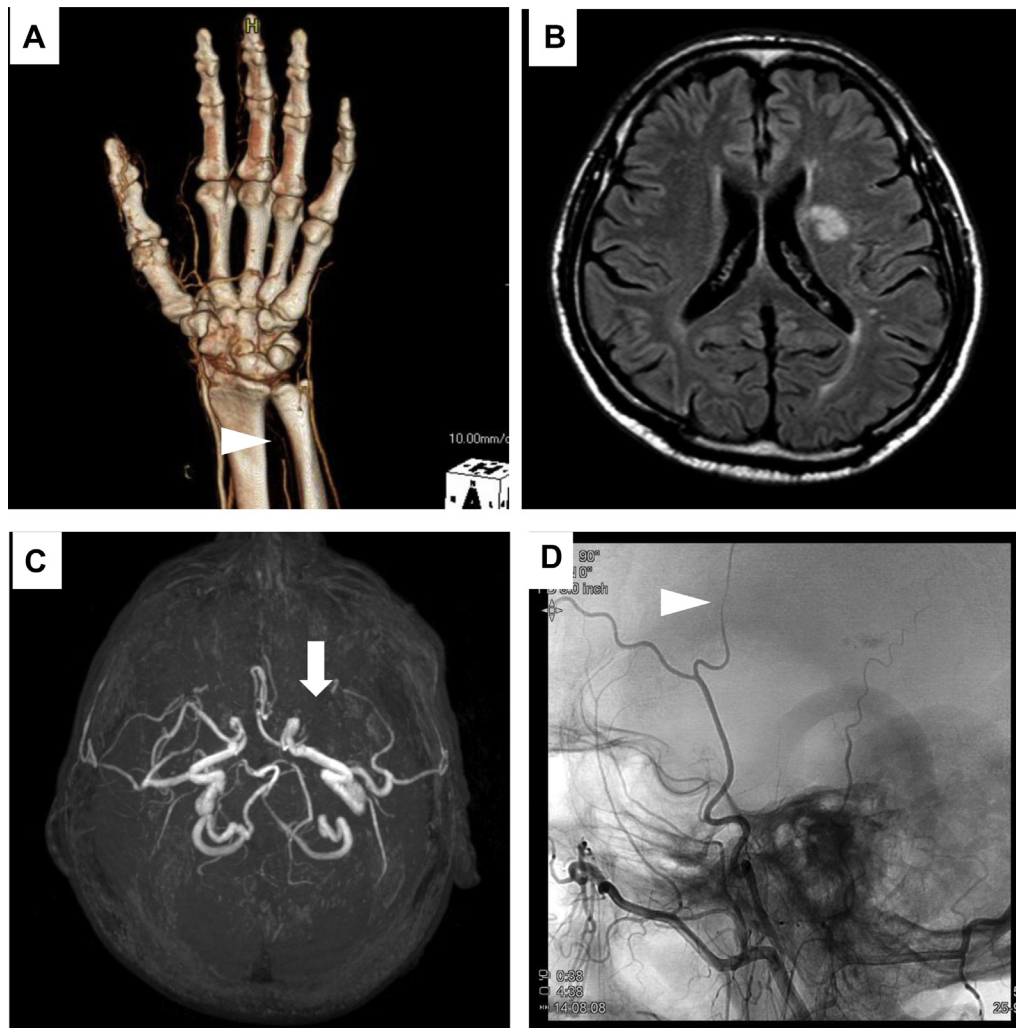


Fig 1. **A**, Upper extremity disease was due to occlusion of ulnar artery and superficial palmar arch (computed tomography angiography). **B**, Branch atheromatous type of cerebral infarction in the left corona radiata area was diagnosed using brain magnetic resonance imaging. **C**, The left middle cerebral artery was occluded in the magnetic resonance angiography (*white arrow*). **D**, A stenosis in the parietal branch of superficial temporal artery was manifested in catheter angiography (*white arrowhead*).

intraoperatively, and we could not use the parietal branch as a donor artery. No skin nodules were noted over the involved artery. Brain magnetic resonance angiography and computed tomography angiography revealed a patent bypass artery within 1 week after surgery and no obvious neurologic findings progressed.

The blood vessels of the parietal branch were histologically examined. The intravascular area was stenotic owing to intimal hyperplasia with smooth muscle cell proliferation (Fig 2, A). No atherosclerotic plaque was found on the vascular wall. Plasma cell, eosinophil, CD3-positive T-cell, and CD20-positive B-cell infiltrations were observed in the outer layer of the vascular hyperplasia (Fig 2, B and C). IgG4 immunohistochemical staining revealed increased IgG4-positive cells (66.7%; Fig 2, D). One year after bypass surgery, Mikulicz's disease was diagnosed according to the biopsy results of the bilaterally swollen salivary glands. Histology of salivary gland tissue revealed a compatible

manifestation to IgG4-RD. The serum IgG4 level was remarkably high (≤ 1080 mg/dL).

The patient was administered low-dose steroid (prednisolone, 0.1 mg/kg/d) to prevent bypass artery occlusion, which resulted in decreased serum IgG4 level and reduced salivary gland volume. The lower and upper extremity disease remained stable and the cerebral bypass was patent at the 2-year follow-up.

DISCUSSION

We report the case of a patient with cerebral infarction before the diagnosis of Mikulicz's disease. He had systemic small-sized arterial occlusive disease of the hands, lower limbs, and superficial temporal artery. The histologic features of the superficial temporal artery included intimal hyperplasia and considerable infiltration of IgG4-expressing plasma cells and eosinophils into the vascular

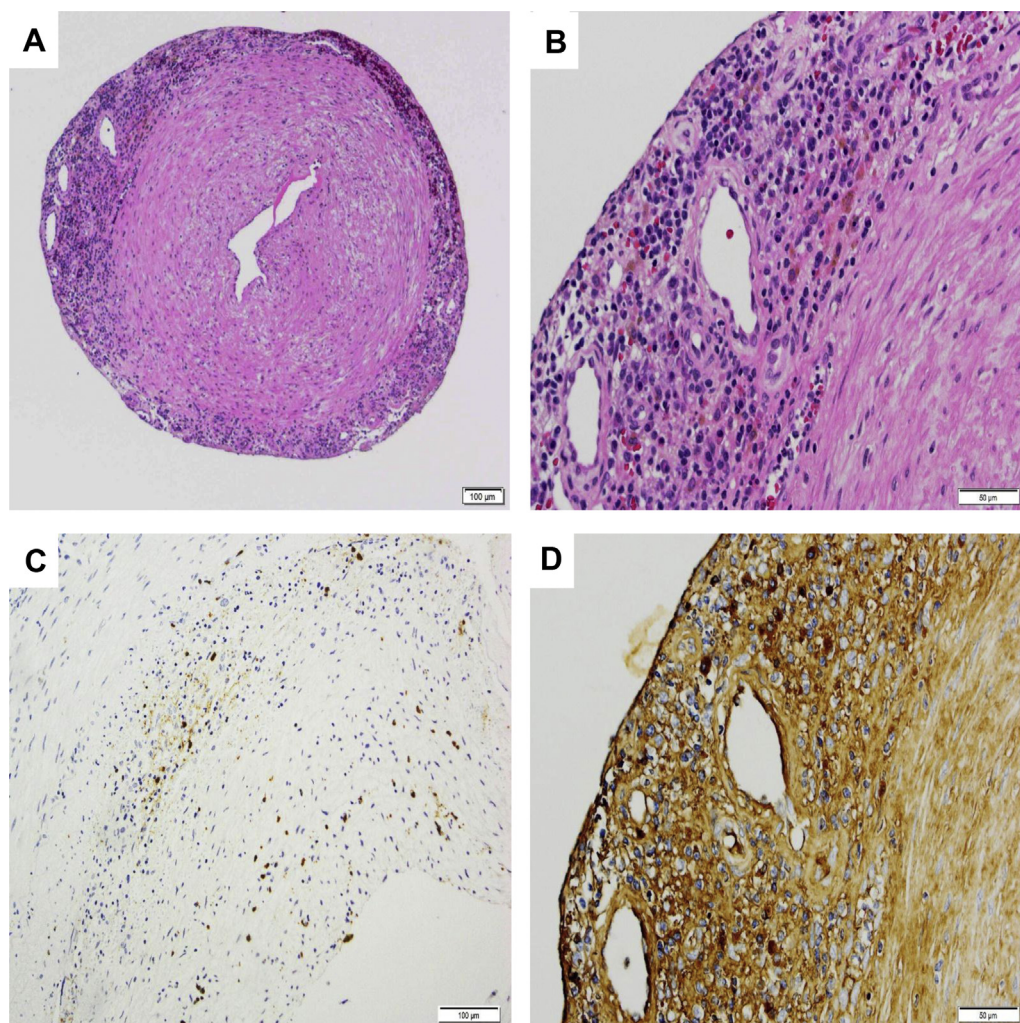


Fig 2. **A**, The blood vessels of the superficial temporal artery had severe stenosis owing to the intimal hyperplasia with smooth muscle cell proliferation (hematoxylin and eosin staining, $\times 100$). **B**, Infiltration of plasma cells with eosinophils was observed in the outer layer of vascular hyperplasia (hematoxylin and eosin staining, $\times 400$). **C**, Eosinophil infiltration was demonstrated using major basic protein staining (staining for major basic protein, $\times 200$). **D**, Increased IgG4-positive cells were observed in immunohistochemical staining for IgG4 (staining for IgG4, $\times 400$).

wall. This is a rare case of IgG4-RD accompanied by small-sized occlusive vasculitis.

IgG4-RD is characterized with more than one organ involvement after a subacute or chronic course. The target organs of IgG4-RD are the pancreas, lacrimal glands, salivary glands, and retroperitoneum. Cardiovascular involvement occurs as aortitis, aortic aneurysm, pericarditis, and pseudotumors surrounding the coronary arteries.¹ IgG4-related periaortitis and periarteritis develop in large- or medium-sized vessels.^{5,6} Small-sized peripheral arteries are rarely involved in IgG4-RD. This case was accompanied by risk factors for atherosclerosis, including diabetes mellitus and history of smoking. Atherosclerosis and Buerger's disease are peripheral occlusive diseases related to smoking.⁸ However, repetitive critical ischemia of the upper and lower limbs was observed after the cessation of smoking. The left and

right ulnar arteries and anterior tibial arteries were occluded without diffuse atherosclerotic lesions. The clinical course of the upper and lower limbs was favorable after continuous low-dose steroid medication therapy. The limb arteries were not histologically examined. We performed superficial temporal artery-middle cerebral artery bypass surgery according to the findings of single-photon emission computed tomography brain blood flow imaging. The genesis of occlusive middle cerebral artery may be due to vasculitis, although we could not rule out an atherosclerotic origin.

Aneurysm formation in the aorta and coronary arteries is a common complication of IgG4-RD.⁹⁻¹¹ Inflammatory abdominal aortic aneurysm is accompanied by a strong IgG4-positive plasma cell infiltration of the aortic wall.⁹ In this case, aneurysm formation was not found in large- and middle-sized arteries; small-sized occlusive lesions

were found in the limbs and cranial vessels. The mechanisms of occlusive vasculitis were not elucidated. Thus, further data collection and analysis are needed.

IgG4-RD is treated with corticosteroids and/or immunosuppressants.¹² Corticosteroids can suppress the active inflammation of aortitis, pericarditis, and pseudotumors.¹ A good response to oral steroid medication therapy was observed in most cases. The corticosteroid dose for IgG4-RD is tailored to individual patient needs, and long-term treatment with low-dose prednisolone decreases disease activity.¹³

CONCLUSIONS

Small-sized occlusive vasculitis owing to IgG4-RD in a patient with Mikulicz's disease is reported. Low-dose corticosteroid therapy is effective in preventing progressive occlusive diseases.

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