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【 CASE REPORT 】

Moyamoya Disease-like Cerebrovascular Stenotic Lesions Are an Important Phenotype of POEMS Syndrome-associated Vasculopathy

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Abstract:

A 41-year-old woman was diagnosed with polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome based on polyneuropathy, hepatosplenomegaly, sclerotic bone lesions, IgA-λ M-protein, and an elevated level of serum vascular endothelial growth factor. One month after the initiation of lenalidomide-dexamethasone with prophylactic aspirin, she developed facial paralysis, dysarthria, and left hemiplegia. Multiple cerebral infarctions and internal carotid artery stenosis were detected. Five months after switching to pomalidomide-dexamethasone, she again developed cerebral infarction. Progressed stenotic lesions in the bilateral internal carotid artery terminal portions were detected, showing a moyamoya disease-like appearance. Quasi-moyamoya disease can be an important phenotype of systemic vasculopathies of POEMS syndrome.

Key words: cerebral infarction, IMiDs, POEMS syndrome, quasi-moyamoya disease, vasculopathy

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Introduction

Polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS) syndrome is characterized by these chief symptoms, which are considered to be associated with an underlying plasma cell disorder and elevated levels of vascular endothelial growth factor (VEGF) (1). In addition to these five main symptoms, disease-related vasculopathy, including thrombosis (2, 3), vascular stenosis (2-6), occlusion/infarction (2-5), and hemorrhage (4, 5) have been reported in the limbs (2, 3), visceral organs (2, 3), and central nervous system (2-6). Although not well-recognized features, these POEMS syndrome-associated vasculopathies (PAV) are important complications. We herein report a case with recurrent cerebral infarctions due to moyamoya disease-like cerebrovascular stenotic lesions (quasi-moyamoya disease) as one of the main features of POEMS syndrome. Quasi-moyamoya disease is a very rare manifestation of POEMS syndrome with only two previous cases reported in the literature to date (4, 5). However, this condition could be one of the phenotypes of PAV, and clinicians should pay attention to the possibility of this disease entity in patients with POEMS syndrome.

Case Report

A 41-year-old woman with no family history of neurological disorders, such as neuropathy or cerebrovascular disease, was referred to our hospital for further examination and treatment of polyneuropathy. Six months prior to presentation at our hospital, she developed muscle weakness in the legs when walking, and began to feel numbness and pain in her feet and lower legs at 4 months prior to presentation. At 3 months prior to presentation, she developed leg edema and visited a local hospital. Although her edema improved after the administration of diuretics, her neuropathic

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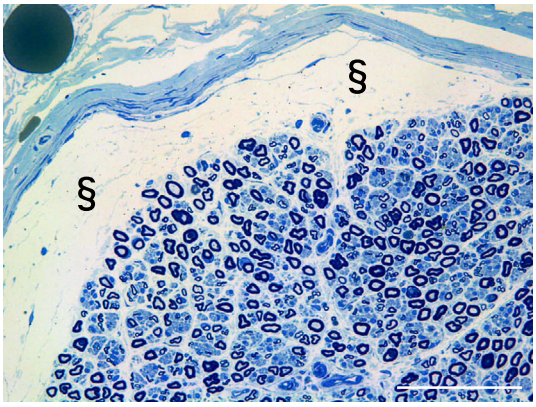

Figure 1. Histopathological picture of a sural nerve biopsy (toluidine blue staining). The histological findings were highly suggestive of POEMS syndrome, such as myelin spheres, indicated distal axonal degeneration due to proximal demyelination, and subperineurial edema (§). Axonal loss was unclear. There was no evident thinning of the myelin sheath or onion bulb formation. Scale bar =100 μm.

symptoms remained. One month prior to presentation, she was referred to the neurology department of the local hospital. She was suspected to have polyneuropathy based on muscle weakness in the legs, reduced tendon reflexes in the extremities, and decreased nerve conduction velocities, and was then admitted to our hospital.

On admission, the physical examination findings were not remarkable except for leg edema. There was no detectable hypertension, skin lesion, or palpable hepatosplenomegaly. Neurological examinations revealed distal dominant muscle weakness in her legs, absent tendon reflexes in the upper and lower extremities, decreased touch, pain, and vibration sensations in the distal legs, numbness and pain in the legs, and disturbed walking with a cane. Laboratory tests revealed an elevated platelet count (450,000/μL, normal 158,000-348,000/μL), IgA-λ M-protein, and elevated serum vascular endothelial growth factor (VEGF, 7,350.0 pg/mL). There was no hyperlipidemia or diabetes mellitus. The cardiac functions and dimensions were normal on echocardiography but mild pericardial effusion was detected. An enhanced computed tomography (CT) scan of the neck, chest, abdomen, pelvis, and femur detected hepatosplenomegaly and sclerotic bone lesions in the lower thoracic spine. No stenotic or occlusive arteriovenous vascular lesions were detected. A nerve conduction test detected lower extremity-dominant amplitude reduction in both motor and sensory nerves with decreased velocities, suggesting sensorimotor polyneuropathy with axonal degeneration. A sural nerve biopsy was performed and the histological findings of axonal degeneration with subperineurial edema were thus identified (Fig. 1). Taken together, a diagnosis of POEMS syndrome was made. Lenalidomide-dexamethasone (Rd) therapy with prophylactic aspirin was started. The affected free light chain (FLC) λ decreased from 34.4 mg/L to 17.7 mg/L after one cycle. Rd therapy was therefore considered to be effective and a second cycle was started as scheduled. On day 6 of the second cycle, she began to feel slight weakness in her left arm. On day 8, she noticed dysarthria and muscle weakness progression in her left arm and leg. These symptoms remained and she visited our hospital on day 9. A neurological examination revealed left unilateral facial paralysis, dysarthria, and mild left hemiplegia. Magnetic resonance imaging (MRI) was performed and multiple cerebral infarctions were detected in the right middle cerebral artery area (Fig. 2A, B). Dual antiplatelet therapy with aspirin and clopidogrel was started. In addition, stenotic lesions at the terminal portion of the bilateral internal carotid artery (ICA) were detected by magnetic resonance angiography (MRA) (Fig. 2C). Although almost all the results of carotid duplex ultrasonography were unremarkable, 1.6 mm intima media thickness was detected in the bifurcation portion of left common carotid artery. POEMS syndrome-associated vasculopathy (PAV) and possible side effects of Rd therapy were suspected, and chemotherapy was switched to pomalidomide-dexamethasone (Pd). After the Pd initiation, hematologic and clinical disease activities were maintained to be plateau state. Five months later, during the sixth cycle of Pd treatment, she developed speaking difficulty and apathy, and new cerebral infarctions were detected in both frontal lobes by MRI (Fig. 2D, E). A progression of stenotic lesions in both sides of ICA terminal portions was demonstrated by MRA, showing a moyamoya disease-like appearance (Fig. 2F). "Moyamoya vessels" (typical collateral vessels observed in moyamoya disease) were not evident in MRA (Fig. 2G). ^{123}I-IMP cerebral blood flow scintigraphy revealed severely decreased tracer uptake in both lobes, especially in the frontotemporal lobe area (Fig. 3). As a result of screening tests for systemic arteriovenous vascular lesions, subclinical bilateral renal infarctions were detected by whole-body enhanced CT scan. Quasi-moyamoya disease, which developed in association with disease progression of PAV, was diagnosed. A direct sequence analysis of the *RNF213* gene for the variant (NM_001256071.2:c.14429G>A:p.Arg4810Lys) was performed and the patient was found to be heterozygous for this variant. The patient was referred to the neurosurgery department for further examination with cerebral angiography to discuss the indications for surgical revascularization. She underwent bilateral superficial temporal artery to MCA (STA-MCA) bypass operations successfully (Fig. 4). After the surgical intervention, she has been in a good clinical state without any new cerebral ischemia attacks or a progression of neuropathy under the additional chemotherapy including daratumumab, lenalidomide, and dexamethasone for 2 years and 5 months.

Discussion

In contrast to moyamoya disease that is defined by "idiopathic" steno-occlusion at the terminal portion of the internal carotid artery, quasi-moyamoya disease is characterized by the presence of underlying primary disease manifesting

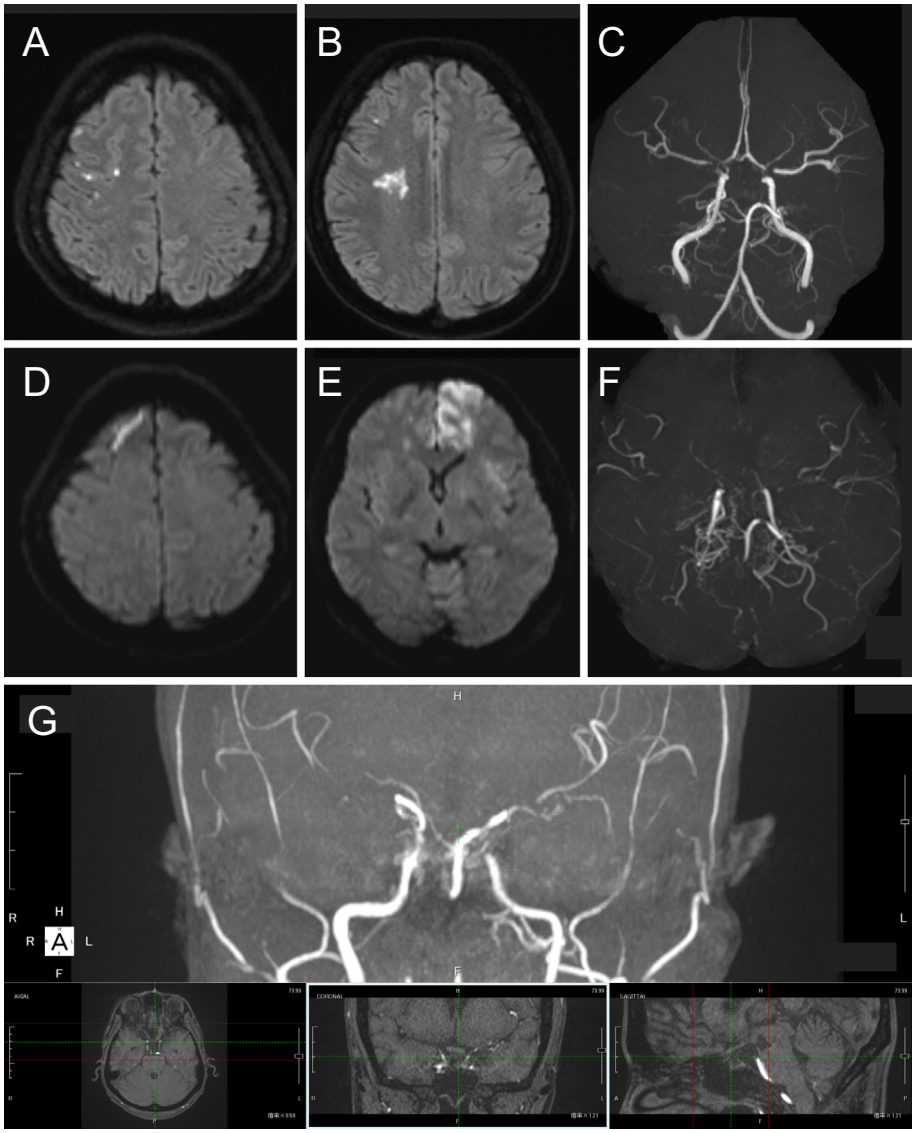

Figure 2. **Diffusion-weighted brain magnetic resonance imaging (MRI) (A, B, D, E) and magnetic resonance angiography (MRA) (C, F, G). (A-C). Images taken at the first episode of stroke. Multiple infarctions in the right middle cerebral artery area (A, B) and stenotic lesion of bilateral internal carotid artery (ICA) in the terminal portion (C) are shown. (D-G). Images taken at the second episode of stroke 5 months after the first episode. These images revealed new cerebral infarctions in both frontal lobes (D, E) and significantly progressed stenotic lesions in the bilateral ICA terminal portions, showing moyamoya disease-like appearance (F). Although coronal maximum intensity projection (MIP) picture focusing on ICA terminal portion was also examined (G), typical collateral vessels (moyamoya vessels) were not evident.**

the same cerebrovascular lesions (7). Various inherited or acquired disorders and conditions have been reported as associated pathologies of quasi-moyamoya disease. A nationwide survey in Japan documented atherosclerosis (29%), Down syndrome (15.1%), von Recklinghausen disease (14%), brain tumor/irradiation (7.5%), autoimmune disease (7.5%), hyperthyroidism (7.5%), and other conditions as associated primary diseases (7).

On the other hand, PAV are regarded as specific types of arteriovenous vascular events, including thrombosis (2, 3), vascular stenosis (2-6), occlusion/infarction (2-5), and hemorrhage (4, 5) in the limbs (2, 3), visceral organs (2, 3), and central nervous system (2-6). The underlying mechanism of PAV has not yet been elucidated. Fu et al. suggested that vasculitis is the dominant mechanism of vasculopathy based on imaging studies showing contrast enhancement without pathological analysis (3). In contrast, some reports indicated that no vasculitis pathology on histological analysis (2, 5). In an autopsy study, Sekiguchi et al. reported that the histological findings of PAV in quasi-moyamoya disease were similar to those of moyamoya disease, showing fibrous intimal thickening and tortuosity of the internal elastic lamina without vasculitis pathology (5).

VEGF is known to play an important role in the vascular

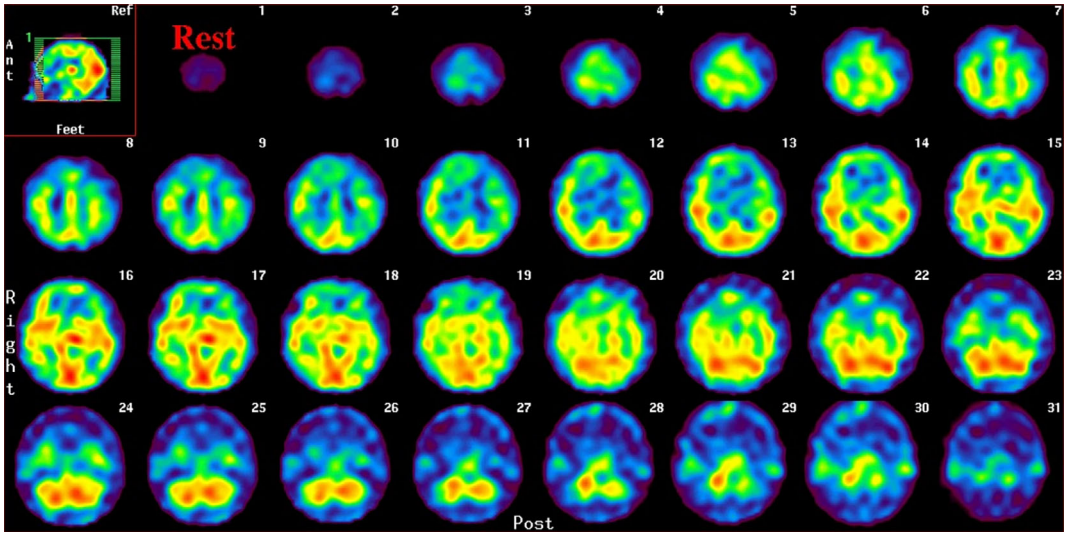

Figure 3. **Axial rainbow color scale images of ^{123}I-IMP cerebral blood flow scintigraphy. The results indicated a diffuse and severe decrease of the cerebral blood flow especially in the frontotemporal lobe area.**

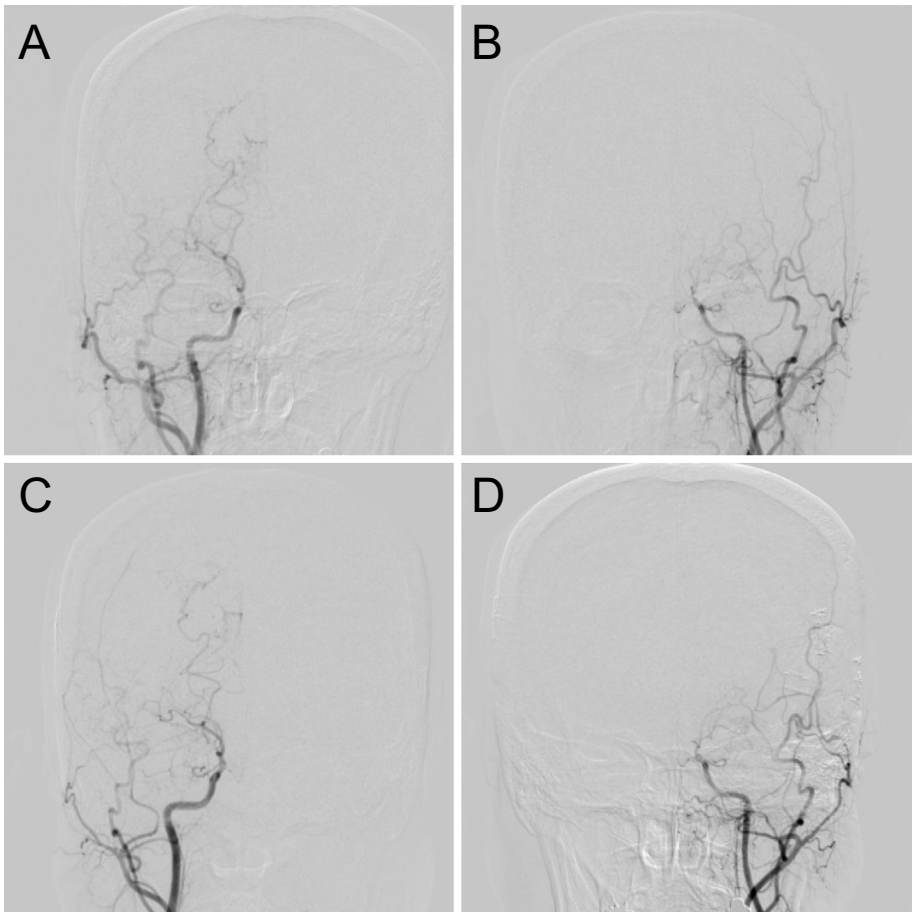

Figure 4. **Digital subtraction angiography (DSA) images of bilateral common carotid artery. DSA images of right (A, C) and left (B, D) common carotid angiography. Images of pre- (C, D) and post- (A, B) bilateral superficial temporal artery to MCA (STA-MCA) bypass operations are presented.**

pathology of POEMS syndrome (1). Interestingly, some studies have demonstrated that there a number of angiogenic agents, including VEGF (8), basic fibroblast growth factor (bFGF) (8), hepatocyte growth factor (HGF) (8, 9), transforming growth factor-β1 (TGF-β1) (8), and granulocyte-colony stimulating factor (G-CSF) (8), are also overex-

pressed in moyamoya disease. Therefore, some angiogenic agents, such as VEGF, could be associated with both diseases, with similar pathological effects in the vessels. This hypothesis would support the observations that the same histopathological findings of involved vasculature were seen in both diseases (5). On the other hand, different mechanisms were also suggested. As shown in the case presentation, rapid progression of ICA terminal stenosis had occurred in only a few months. It is possible to postulate that additional pathological mechanisms in POEMS syndrome have made vascular stenosis worsen more rapidly than in idiopathic moyamoya disease and a few months was not long enough for collateral circulation system to develop sufficiently.

Furthermore, this immature collateral circulation system might have been affected by chemotherapy, resulting in the patient's pathology. Anti-plasma cell chemotherapy is considered to be effective for POEMS syndrome in principle (1). However, because VEGF is important in angiogenesis in POEMS syndrome (1), anti-plasma cell chemotherapy might have caused collapse of immature collateral circulation system by decreasing the serum level of VEGF and might have affected the ischemic mechanisms in the present case. Therefore, it may be important to discuss how to use optional anti-ischemic agents appropriately, such as antiplatelet, anticoagulant, and possible vasodilation agents, when administering the chemotherapeutic drugs for POEMS patient with stenotic vascular lesion(s).

POEMS syndrome-associated quasi-moyamoya disease is extremely rare, and only two cases have been reported to date (4, 5). Yamaguchi et al. reported a 49-year-old woman with plasmacytoma-associated POEMS syndrome, who developed quasi-moyamoya disease-related intracranial hemorrhage during the disease remission period 5 years after radiation therapy for plasmacytoma (4). Sekiguchi et al. reported a 45-year-old man with plasmacytoma-associated POEMS syndrome, who developed quasi-moyamoya disease-related recurrent cerebral infarction while chemotherapy for POEMS syndrome failed because of adverse effects (5). These reports suggest that quasi-moyamoya disease can progress during the "treatment cessation period" (5) and can also progress during the "remission period" of POEMS syndrome (4), resulting in cerebral stroke. Therefore, our case is the first report of POEMS syndrome-associated quasi-moyamoya disease that progressed and resulted in recurrent cerebral infarction despite ongoing chemotherapy.

Our patient was treated with immunomodulatory drugs (IMiDs), such as lenalidomide or pomalidomide. Thalidomide and its analogs, lenalidomide and pomalidomide, are referred to as IMiDs and have been reported to have multiple actions with direct and/or indirect antitumor effects (10, 11). These actions include immunomodulatory, antiangiogenic, antiinflammatory, and antiproliferative effects (10, 11). These IMiDs are currently considered to be fundamental antimyeloma agents with a high efficacy and are now widely used (12). Furthermore, as most POEMS syndrome patients have the same underlying plasma cell pathology as myeloma, IMiDs have also become promising key drugs for its treatment (1, 13). Our patient, however, showed a progression of quasi-moyamoya disease and developed recurrent cerebral ischemic attacks despite effective treatment with IMiDs. As the 5-year risk of cerebral infarction in POEMS syndrome has been reported to be as high as 13.4% (14) and IMiDs therapy combined with dexamethasone is known to be associated with increased risk of venous thromboembolism (15), it is recommended to add antiplatelet therapy when treating patients with IMiDs (15). However, antithrombotic therapy may be insufficient to completely prevent cerebral infarction (6), because some reports have indicated that patient with POEMS syndrome could develop cerebral infarction despite prophylactic antithrombotic therapy during the period of treatment with IMiDs and/or dexamethasone (6, 16). As in these cases, our patient also developed cerebral infarction even with prophylactic aspirin treatment. IMiDs therapy was therefore thought to be associated with the underlying mechanism of cerebral infarction in our patient to some degree. Hence, an appropriate assessment of systemic vascular status, including cerebral MRI/MRA before treatment initiation, is necessary for the risk management of PAV. Careful monitoring of vascular status after initiating treatment is also recommended, because treatment regimens with IMiDs are being used more frequently (1, 13).

Another possible pathological mechanism of cerebrovasculopathy in this case might be associated with p.Arg4810 Lys variant in *RNF213* gene. Because this variant was known as susceptibility variant for Moyamoya disease (17) and other intracranial artery stenosis (18), progressive cerebrovasculopathies in this patient might have been attributable to this gene variant to some extent.

In conclusion, moyamoya disease-like cerebrovascular stenotic lesions (quasi-moyamoya disease) can be one phenotype of systemic vasculopathy of POEMS syndrome. A patient with this condition can develop cerebral infarction even during the period of ongoing effective chemotherapy with prophylactic antiplatelet agents. Screening cerebral MRI/MRA examinations at the diagnosis of POEMS syndrome and careful vascular monitoring after initiation of treatment are recommended for all patients, especially when treating patients with IMiDs.

The authors state that they have no Conflict of Interest (COI).

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