CASE REPORT

Nagoya J. Med. Sci. **85**. 141–149, 2023
doi:10.18999/nagjms.85.1.141

Surgical revascularization for quasi-moyamoya disease associated with polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome: a case report and literature review

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ABSTRACT

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare multisystem disease characterized by plasma cell dyscrasia and overproduction of vascular endothelial growth factor, which is related to disease activity. Recent treatment strategies have improved survival of patients suffering from this disorder; however, ischemic stroke remains a poor prognostic factor. POEMS patients with ischemic stroke frequently develop cerebral large artery stenosis/occlusion, followed by progressive stroke. Post literature review, we present an ischemic stroke case of quasi-moyamoya disease linked with this syndrome that was successfully treated with surgical revascularization. A 41-year-old woman diagnosed with POEMS syndrome developed progressive ischemic stroke due to quasi-moyamoya disease, despite decreased vascular endothelial growth factor level with lenalidomide and dexamethasone treatment. She underwent superficial temporal artery to middle cerebral artery bypass with encephalo-duro-myo-synangiosis bilaterally. The postoperative course was uneventful. Two years and five months after the stroke, neuroimaging demonstrated bypass patency, neovascularization after encephalo-duro-myo-synangiosis, and no recurrence of stroke. Our case is the first to report successful surgical revascularization for a POEMS patient. Surgical revascularization may be a useful treatment option for patients with quasi-moyamoya disease associated with POEMS syndrome, especially for those who develop refractory ischemic stroke despite reduced vascular endothelial growth factor level.

Keywords: cerebral infarction, cerebral revascularization, Crow–Fukase syndrome, STA-MCA anastomosis, vascular endothelial growth factor

Abbreviations:
ICA: internal carotid artery

Received: January 14, 2022; accepted: February 24, 2022
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^{123}I-IMP SPECT: N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography
MCA: middle cerebral artery
MRA: magnetic resonance angiography
STA: superficial temporal artery
POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
VEGF: vascular endothelial growth factor

INTRODUCTION

Polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes (POEMS) syndrome is a rare paraneoplastic syndrome associated with plasma cell dyscrasia.[1,2] Mandatory major criteria for the syndrome are polyneuropathy and monoclonal plasma cell-proliferative disorder. Other major criteria are the presence of Castleman disease, sclerotic bone lesions and vascular endothelial growth factor (VEGF) elevation. Minor criteria include organomegaly, extravascular volume overload, endocrinopathy, skin changes, papilledema, and thrombocytosis/polycythemia. A diagnosis of POEMS syndrome is made when both of the mandatory major criteria, one of the other major criteria, and one of the minor criteria are present.[2] Recent treatment strategies have favorably improved survival of POEMS patients.[3] However, prognosis remains extremely poor for POEMS patients who developed ischemic stroke.[4]

To date, there has been no report of successful surgical revascularization for POEMS patients who developed ischemic stroke. Herein, we present an ischemic stroke case of quasi-moyamoya disease associated with POEMS syndrome, who successfully underwent surgical revascularization, and we review the literature on patients with quasi-moyamoya disease associated with POEMS syndrome.

CASE REPORT

A 41-year-old woman was admitted to the department of neurology at our institution with a 6-month history of numbness and weakness in the lower extremities. The patient had no history of smoking, drinking alcohol, taking any medications, diabetes mellitus and dyslipidemia, and no relevant family history. Physical and neurological examinations showed symmetrical pitting edema, lower-extremity hypoesthesia/motor weakness, and absence of deep tendon reflexes. Nerve conduction studies demonstrated demyelinating polyneuropathy. Computed tomography revealed hepatomegaly, splenomegaly, and sclerotic bone lesions. Serum VEGF was high (7,350.0 pg/ml; normal < 38.3 pg/ml), and serum immunoelectrophoresis disclosed IgA lambda monoclonal gammopathy. Thus, the patient was diagnosed with POEMS syndrome.[5] Lenalidomide and dexamethasone treatment was started. Serum VEGF level decreased to 1,920.0 pg/ml after this therapy.

One month later, the patient presented with left facial palsy and hemiplegia. Diffusion-weighted imaging revealed acute cerebral infarction lesions, including the right centrum semiovale (Fig. 1A). Magnetic resonance angiography (MRA) showed stenosis at the bilateral terminal internal carotid arteries (ICA) (Fig. 1A). Dual antiplatelet therapy with aspirin (100 mg/day) and clopidogrel (75 mg/day) was started.

Five months later, the patient suddenly became apathetic and somnolent. The Mini-Mental State Examination score was 16/30. Diffusion-weighted imaging showed acute cerebral infarction with a focus on the left frontal lobe (Fig. 1B). MRA revealed loss of signal intensity at the bilateral terminal ICAs, proximal anterior cerebral arteries and proximal middle cerebral arteries (MCA)

(Fig. 1B). Carotid ultrasonography revealed no specific findings, except for maximal intima-media thickness of the left common carotid artery (1.5 mm). The patient was referred to our department for evaluations of progressive stroke. Angiography detected terminal ICA occlusion and presence of basal moyamoya vessels bilaterally; the patient was diagnosed as having quasi-moyamoya disease associated with POEMS syndrome (Fig. 2A, 2B). N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT) showed decreased cerebral blood flow in the anterior cerebral artery and MCA territories bilaterally, predominantly on the left (Fig. 2C). To prevent further cerebral ischemic stroke, left superficial temporal artery to MCA bypass (STA–MCA bypass) with encephalo-duro-myo-synangiosis was conducted. One month after the surgery, right STA-MCA bypass with encephalo-duro-myo-synangiosis was performed. The STA was partially resected for histological analysis. The postoperative course was uneventful. The patient's consciousness recovered; the postoperative Mini-Mental State Examination score raised to 25/30. Left facial palsy and hemiplegia gradually improved. Histologically, the STA showed severe intimal thickening with fibrous proliferation (Fig. 3). The vessel wall had no inflammation, cholesterol crystals, or calcification.

Two years and five months after the last stroke, magnetic resonance imaging demonstrated no recurrence of cerebral infarction (Fig. 4A). Angiography revealed the bypass patency and neovascularization after encephalo-duro-myo-synangiosis bilaterally (Fig. 4B, 4C). ^{123}I-IMP SPECT showed improved cerebral blood flow in the bilateral MCA territories (Fig. 4D). Lenalidomide

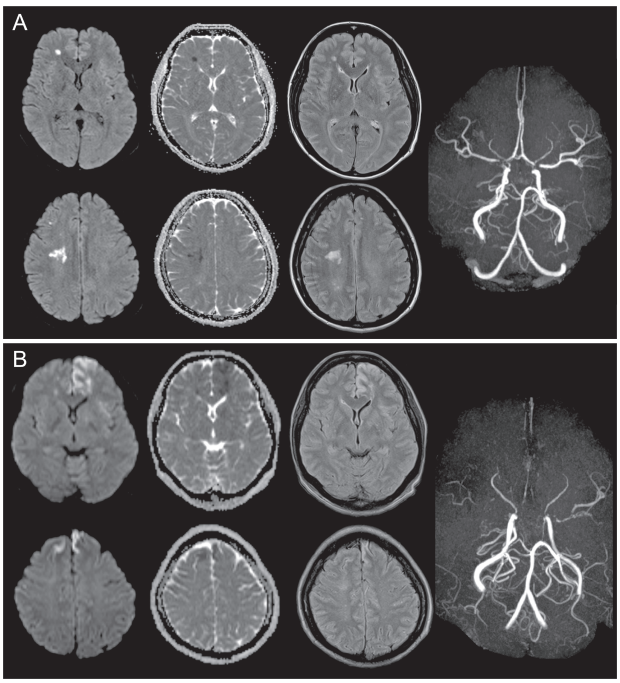

Fig. 1 Preoperative magnetic resonance imaging including diffusion-weighted imaging, apparent diffusion coefficient maps, fluid-attenuated inversion recovery imaging, and magnetic resonance angiography (MRA)

Fig. 1A: Magnetic resonance imaging at the first stroke onset. MRA demonstrates stenosis at the bilateral terminal internal carotid arteries (ICA).

Fig. 1B: Magnetic resonance imaging at the second stroke onset. MRA shows loss of signal intensity at the bilateral terminal ICA, proximal anterior cerebral arteries, and proximal middle cerebral arteries.

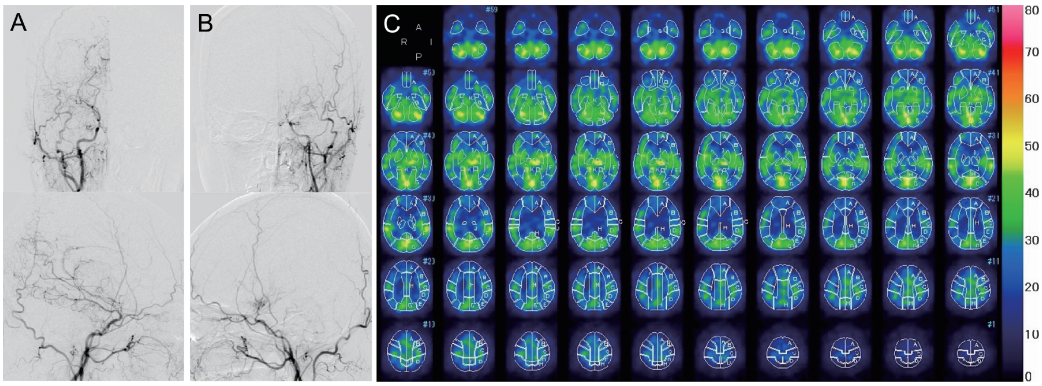

Fig. 2 Preoperative cerebral angiography (A, B) and N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT) imaging (C)

Fig. 2A, 2B: Preoperative common carotid angiography shows the terminal internal carotid artery (ICA) occlusion and presence of the basal moyamoya vessels bilaterally.

Fig. 2C: Preoperative ^{123}I-IMP SPECT imaging shows decreased cerebral blood flow in the bilateral ICA territories, predominantly on the left.

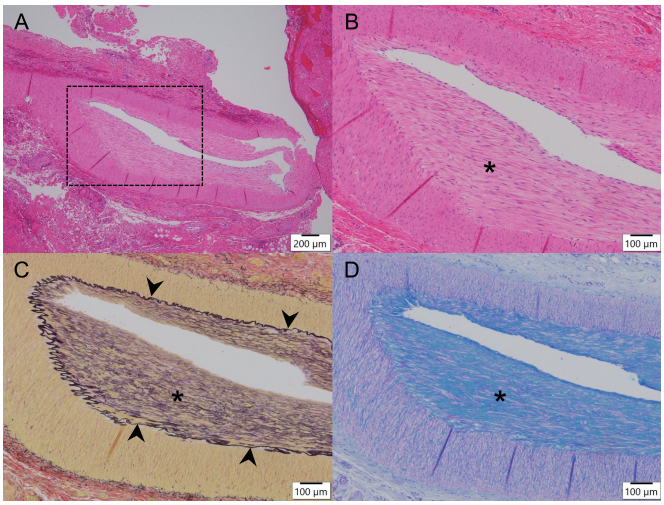

Fig. 3 Histopathological pictures of resected superficial temporal artery (A, B: Hematoxylin-Eosin stain, C: Elastica van Gieson stain, D: Alcian Brue PAS stain)

Stenotic superficial temporal artery without evident infiltration of inflammatory cells is shown (A). Dotted rectangle in A indicates the area of enlarged view shown in pictures B, C, and D. Asterisks in pictures B, C, and D indicate significantly thickened intima. Internal elastic membrane (arrowheads) was preserved (C). Alcian Brue-positive acid mucopolysaccharide deposition in the thickened intima was detected (D).

and dexamethasone treatment successfully had suppressed serum VEGF level. The patient had no ischemic stroke events clinically after the last stroke.

This study was approved by the institutional review board, and a written informed consent for treatment was obtained from the patient.

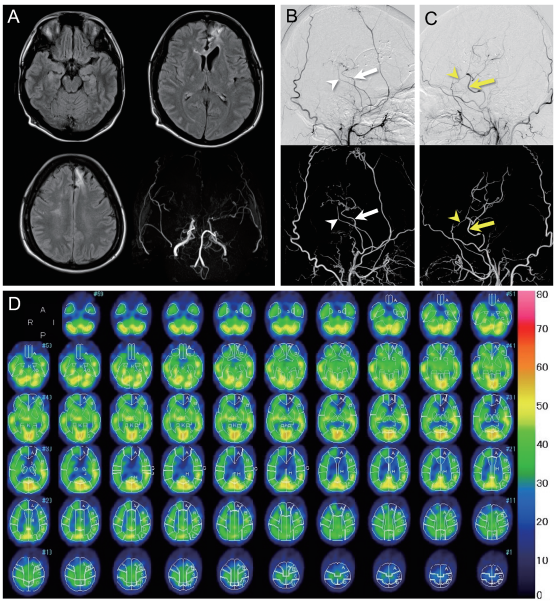

Fig. 4 Postoperative magnetic resonance imaging (A), cerebral angiography (B), and N-isopropyl-p-[^{123}I]-iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT) imaging two years and five months after the last stroke

Fig. 4A: Postoperative magnetic resonance imaging shows no recurrence of ischemic stroke. In magnetic resonance angiography, bilateral superficial temporal arteries and right middle meningeal artery were observed.

Fig. 4B: Postoperative lateral views of right external carotid artery angiography and three-dimensional rotational angiography. Bypass patency (white arrows) and neovascularization via the right middle meningeal artery (white arrowheads) were identified.

Fig. 4C: Postoperative lateral views of left external carotid artery angiography and three-dimensional rotational angiography. Bypass patency (yellow arrows) and neovascularization via the left deep temporal artery (yellow arrowheads) were identified.

Fig. 4D: Postoperative ^{123}I-IMP SPECT imaging shows improved cerebral blood flow in the bilateral middle cerebral artery territories.

DISCUSSION

POEMS syndrome is a rare multisystem, autoinflammatory paraneoplastic condition, defined by the presence of inflammatory peripheral neuropathy and a monoclonal plasma cell disorder.[1,2] The pathogenesis of POEMS syndrome is not fully understood. Monoclonal plasma cell dyscrasia may influence an overproduction of proinflammatory cytokines with downstream effects.[2] VEGF—a potent multifunctional cytokine responsible for angiogenesis, microvascular hyperpermeability, and inflammation of vascular endothelial cells—is markedly elevated in untreated POEMS compared with other hematologic malignancies and inflammatory neuropathies. Therefore, upregulated VEGF is believed to play a pivotal role; it correlates with disease activity, prognosis, and response to therapy.[6,7] POEMS syndrome is a potentially fatal disease, and patients' quality of life deteriorates due to progressive disabling neuropathy, massive pleural effusion or ascites, or thromboembolic events. In the 1980s, the mean survival time was 33 months in 34 patients who were mainly treated with corticosteroids.[8] However, recent therapeutic strategies provide superior outcomes, with overall 6-year progression-free survival of more than 50%.[3] The 5-year progression-free

survival rate is 88% in patients who achieved a complete hematologic response, and 50% including patients who do not achieve a complete hematologic response. For patients with a dominant sclerotic plasmacytoma, the first-line therapy is radiation therapy.[2] Patients with diffuse sclerotic lesions or disseminated bone marrow involvement, and those who have disease progression 3–6 months after radiation therapy, should receive systemic therapy, including alkylator-based therapy and autologous peripheral stem cell transplantation, lenalidomide, thalidomide, or bortezomib.[2] The response criteria is defined as follows: complete response (the normalization of the serum VEGF level), improvement (50% reduction from the baseline serum VEGF level), and progression (50% increase from the lowest serum VEGF level).[2]

Recent reports have documented ischemic stroke occurring in 8%–13% of patients diagnosed with POEMS syndrome.[9,10] A retrospective cohort study demonstrated 93% of ischemic stroke events occurred before or immediately after the diagnosis of POEMS symptoms, implying that ischemic stroke events occurred in POEMS patients not being treated effectively.[9] A recent review article has reported death within 2 years after the stroke events in 10 (55.6%) of 18 POEMS patients with ischemic stroke; development of ischemic stroke is a predictor of unfavorable prognosis.[4] POEMS patients with ischemic stroke are highly associated with intracranial large artery stenosis/occlusion, which can lead to multifocal, progressive, and refractory stroke.

To date, only two cases that developed quasi-moyamoya disease associated with POEMS syndrome have been described (Table 1).[11,12] Yamaguchi et al documented a 44-year-old woman with a 5-year history of POEMS syndrome who presented with left putaminal hemorrhage.[11] The serum VEGF level was well controlled after initial treatment. MRA showed progressive loss of signal intensity at the terminal ICAs and MCAs bilaterally, compared with 5 years earlier. Angiography detected bilateral terminal ICA occlusion, M1 occlusion, and basal moyamoya vessels. The authors concluded that the hemorrhage was caused by rupture of a fragile basal moyamoya vessel. Conservative therapy was applied, and no rebleeding was observed 2 years after the hemorrhage. Sekiguchi et al described a 45-year-old man with a 1-year history of POEMS syndrome, who presented with progressive cerebral infarction at the left frontal lobe.[12] Bortezomib with dexamethasone treatment, and thalidomide treatment failed due to their side effects. MRA demonstrated progressive loss of signal intensity at the terminal ICAs, anterior cerebral arteries, and MCAs bilaterally over 2 months. Angiography revealed bilateral terminal ICA occlusion, A1 occlusion, M1 occlusion, and basal moyamoya vessels. Left STA-MCA bypass with encephalo-duro-arterio-myo-synangiosis was conducted. However; the patient developed acute exacerbation of heart failure and fatal recurrent ischemic stroke; he died 4 months after surgery. In all three cases (including our case), intracranial large artery stenosis/occlusion and moyamoya vessels developed progressively within relatively short time (Table 1). In our case, therapeutic improvement (50% reduction from the baseline serum VEGF level) was obtained after lenalidomide and dexamethasone treatment. However, the normalization of the serum VEGF level was not achieved, which may have caused the progression of intracranial large artery stenosis/occlusion and moyamoya vessels. Thus, careful angiographic monitoring will be required for patients with POEMS who suffered ischemic stroke. A review article described that 18 (64.3%) of 28 POEMS cases with ischemic stroke involved intracranial large artery stenosis/occlusion.[4] Based on contrast enhancement magnetic resonance imaging findings, some researchers have speculated that "vasculitis" was the main mechanism underlying large artery stenosis/occlusion associated with POEMS syndrome.[4,13] However, based on histopathological findings, Sekiguchi et al. revealed that intracranial large artery stenosis/occlusion associated with POEMS syndrome resulted from duplication of internal elastic lamina and marked fibrous thickening localized to intima, which was similar to moyamoya disease.[12] Additionally, there was no evidence of vasculitis, including inflammatory cell infiltration, multinucleated giant cells, or granulomas.[12]

In our case, histopathological analysis of the resected STA revealed an obvious stenotic lesion with significantly thickened intima (Fig. 3). This finding indicates that not only the intracranial arteries but also the extracranial arteries can be affected in patients with quasi-moyamoya disease associated with POEMS syndrome, which in turn, suggests the existence of underlying systemic vasculopathy.[5] Elevated systemic VEGF level induces hypertrophy/proliferation of endothelial

Table 1 Summary of case reports of quasi-moyamoya disease associated with POEMS syndrome

	Yamaguchi et al[11] (2016)	Sekiguchi et al[12] (2020)	The current case
Age (years)/sex	49/female	45/male	41/female
POEMS syndrome			
Treatment	Radiation therapy	Bortezomib and dexamethasone followed by thalidomide[a]	Lenalidomide and dexamethasone
Serum VEGF level	Favourably controlled	Not controlled	Favourably controlled
Stroke			
Time after POEMS diagnosis	5 years	1 year	1 month
Type	Left putaminal haemorrhage	Progressive ischaemia at left MCA territory	Progressive ischaemia at bilateral ACA and MCA territories
Symptoms	Right hemiparesis	Right recurrent hemiparesis	Left hemiparesis/ apathy
Quasi-moyamoya disease			
Diagnosis	MRA and angiography	MRA and angiography	MRA and angiography
Treatment			
Medication	None	Cilostazol	Aspirin and clopidogrel
Surgery	None	Left STA-MCA bypass and EDAMS	Bilateral STA-MCA bypass and EDMS
Histopathological study	None	Yes[b]	None
Recurrent stroke	None at least 2 years	Yes	None at least 2 years and 5 months
Survival time after the last stroke	More than 2 years	6 months	More than 2 years and 5 months

[a] Bortezomib and dexamethasone therapy and thalidomide therapy failed due to their side effects.
[b] Histopathological findings revealed duplication of internal elastic lamina and marked fibrous thickening localised to intima of bilateral proximal MCAs which is similar to moyamoya disease. There was no evidence of vasculitis, including inflammatory cell infiltration, multinucleated giant cells or granulomas and no lipid-rich plaque suggesting atherosclerosis.
ACA: anterior cerebral artery
EDAMS: encephalo-duro- arterio-myo-synangiosis
EDMS: encephalo-duro-myo-synangiosis
MCA: middle cerebral artery
MRA: magnetic resonance angiography
POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes
STA: superficial temporal artery
VEGF: vascular endothelial growth factor

cells, which may lead to vessel stenosis/occlusion systemically.[2,11] VEGF-induced angiogenesis may result in fragile moyamoya vessels.[11] Thus, the intracranial large artery stenosis/occlusion associated with POEMS syndrome can be "irreversible" and "progressive" in nature. To prevent stroke events (progression of quasi-moyamoya disease), decreased serum VEGF level should be mandatory. In all three cases, therapeutic efficacy for POEMS syndrome may have affected the patient's prognosis (Table 1). According to a review article,[4] intracranial large artery stenosis/occlusion in POEMS patients who developed ischemic stroke was primarily diagnosed with MRA, which may have overlooked occurrence of moyamoya vessels (diagnosis of quasi-moyamoya disease). In all three cases, quasi-moyamoya disease was diagnosed based on cerebral angiography (Table 1). There can be a certain number of quasi-moyamoya disease associated with POEMS syndrome.

Surgical revascularization for quasi-moyamoya disease has been reported useful in patients with Graves' disease and Down syndrome.[14,15] To the best of our knowledge, our case is the first to report successful surgical revascularization for quasi-moyamoya disease associated with POEMS syndrome. We applied surgical revascularization for our case because progressive cerebral infarction and intracranial large artery stenosis/occlusion occurred despite satisfactory control of the serum VEGF level. Mid-term follow-up results showed favorable outcome. Based on postoperative neuroimaging findings, bilateral STA-MCA bypass with encephalo-duro-myo-synangiosis will contribute to the prevention of recurrent ischemic stroke. Therefore, surgical revascularization may be a useful treatment option for patients with quasi-moyamoya disease associated with POEMS syndrome, especially for those who develop progressive stroke despite well-controlled serum VEGF level.

CONCLUSION

Patients with POEMS syndrome who have undergone ischemic stroke are frequently associated with intracranial large artery stenosis/occlusion, which can cause progressive stroke. Thus, ischemic stroke remains a poor prognostic factor. To the best of our knowledge, the present case is the first to demonstrate successful surgical revascularization of quasi-moyamoya disease associated with POEMS syndrome. Hence, surgical revascularization is a potentially useful treatment option for patients with quasi-moyamoya disease associated with POEMS syndrome, especially for those who suffered progressive stroke despite well-controlled serum VEGF levels.

AUTHOR CONTRIBUTION

YK and YH contributed equally as first authors to this work.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to disclose.

ETHICS APPROVAL

This study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments.

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