Coexistence of Quasi-moyamoya Disease and POEMS Syndrome in a Patient with Intracranial Hemorrhage: A Case Report and Literature Review

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POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare paraneoplastic syndrome elicited by plasma cell dyscrasia. Its clinical manifestations are multiple and stroke is not a recognized feature. A 44-year-old woman with a 3-month history of bilateral lower extremity sensorimotor disturbance was admitted to our hospital. Examinations revealed polyneuropathy, organomegaly, hypothyroidism, monoclonal gammopathy, pelvic plasmacytoma, and elevated serum vascular endothelial growth factor (VEGF) levels. A diagnosis of POEMS was made. Her condition was improved by radiation therapy of her pelvic plasmacytoma and she continued to be seen on an outpatient basis. Five years after her first admission she was re-admitted with sudden-onset right hemiparesis. A brain computed tomography (CT) scan revealed a left intracranial hemorrhage and magnetic resonance (MR) angiography and cerebral angiography showed occlusion of the proximal portion of the bilateral middle cerebral artery and narrowing of the bilateral internal carotid artery at the terminal portion; moyamoya vessels were seen. This is the first report of a patient whose intracranial hemorrhage was attributable to quasi-moyamoya disease associated with POEMS syndrome. We suggest that the POEMS syndrome be ruled out in the differential diagnosis of patients presenting with atypical stroke, multivessel stenotic lesions (moyamoya vessels), and polyneuropathy.

Keywords: POEMS syndrome, VEGF, quasi-moyamoya disease

Introduction

POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes) syndrome is a rare paraneoplastic syndrome due to plasma cell dyscrasia.1-3 Major clinical manifestations of this syndrome are captured by the acronym POEMS; they include polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes.2-5 Stroke is not a recognized feature of this syndrome. This is the first report of a patient with sudden-onset intracranial hemorrhage attributable to quasi-moyamoya disease associated with POEMS syndrome.

Case Report

A 44-year-old woman with a 3-month history of lower limb hypesthesia and paralysis was admitted to our hospital. The medical history of the patient was unremarkable. Physical examination revealed cervical lymph node swelling and pretibial edema. Neurological examination showed lower limb motor weakness, sensory loss, and absent distal reflexes. As electrophysiologic tests disclosed a polyneuropathy pattern we suspected chronic inflammatory demyelinating polyneuropathy. Abdominal computed tomography (CT) showed a pelvic tumor (Fig. 1A), hepatomegaly, splenomegaly, para-aortic lymph node swelling and ascites. CT-guided biopsy of the tumor revealed plasmacytoma (Fig. 2). The serum vascular endothelial growth factor (VEGF) level was 814 pg/ml. Serum immunoelectrophoresis showed monoclonal gammopathy (IgG); the hormonal values were indicative of hypothyroidism. Under a diagnosis of POEMS syndrome, she underwent radiation therapy (46 Gy delivered in 23 fractions) for pelvic plasmacytoma. Pelvic plasmacytoma gradually became smaller and changed into osteosclerotic lesion (Fig. 1B). Hepatomegaly, splenomegaly, para-aortic lymph node swelling, and monoclonal gammopathy were improved. The serum VEGF level decreased to 406 pg/ml. Her condition improved and she was discharged. During this period, magnetic resonance (MR) angiography taken for headache revealed a narrowing of the proximal portion of the bilateral middle cerebral artery and the terminal portion of the internal carotid artery (Fig. 3A). She had no cerebral ischemic symptom and no family history of moyamoya disease. MR angiography was not followed up since headache was mild and improved.

Five years later, she was readmitted with a chief complaint of sudden-onset right hemiparesis. A brain CT scan showed left intracranial hemorrhage (Fig. 3B). MR angiography and cerebral angiography revealed progression of vessel stenosis, development of leptomeningeal anastomosis and moyamoya vessels (Fig. 3C–F). Moyamoya vessels were less than a typical moyamoya disease, and collateral circulation from the external carotid artery was not detected. Cerebral microbleeds were not detected. Single photon emission tomography (SPECT) using N-isopropyl-4 iodoamphetamine (123I-IMP) obtained on the 13th hospital day showed reduction of the cerebral blood flow (CBF) in the left frontoparietal

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cortex, left regional temporo-occipital cortex, and right cerebellum (Fig. 3G). Complete blood cell count, basic metabolic panel and coagulation parameters revealed normal findings. The serum VEGF level was 27.9 pg/ml. No recurrence of monoclonal gammopathy was observed after initial therapy. Disease progression of POEMS syndrome was thought to be negative in laboratory data. Although we thought that her hemorrhage was due to hemodynamic stress she was treated conservatively because the appropriate treatment of quasi-Moyamoya disease remains to be determined.3) She was transferred to a rehabilitation center and in the course of two-year follow-up she suffered no rebleeding.

Discussion
POEMS syndrome and cerebrovascular disease

POEMS syndrome have been also called Crow-Fukase syndrome, Takatsuki syndrome or PEP (plasma cell dyscrasia, endocrinopathy, and polyneuropathy) syndrome. POEMS syndrome is a very rare disease; a 2003 survey showed an incidence of approximately 0.3/100,000 Japanese.1) Of 99 patients with POEMS syndrome contained in the Mayo Clinic database, 18 had experienced venous (n = 10) and/or arterial (n = 11) thrombotic events manifesting as myocardial infarction, stroke, and Budd-Chiari syndrome.4) The literature on POEMS syndrome associated with cerebrovascular disease documents 23 patients and most of these presented with major vessel stenosis or occlusion (Table 1).2,5-15) The 5-year risk for stroke in patients with POEMS syndrome is 13.4%. According to Dupont et al.2) POEMS syndrome is accompanied by multi-vessel stenosis and typically leads to vascular anomalies. The elevation of plasma and serum VEGF levels is a characteristic of POEMS syndrome and included in its diagnostic criteria. Plasma VEGF levels of 200 pg/ml were 95% specific and 68% sensitive for a diagnosis of POEMS syndrome.1)

Quasi-moyamoya disease and moyamoya disease

In quasi-moyamoya disease, vessel stenosis or occlusion is accompanied by an abnormal vascular network associated with an underlying disease.16) The annual incidence of quasi-moyamoya disease is 0.11/100,000; its prevalence is 0.34/100,000.17) Underlying diseases are atherosclerosis (29%), Down syndrome (15.1%), von Recklinghausen disease (14%), brain tumor/irradiation (7.5%), autoimmune disease (7.5%), and hyperthyroidism (7.5%).18) The ring finger protein (RNF213) is a susceptibility gene for moyamoya disease.19) Although the homozygous c.14576G>A variant of RNF213 predicts the early onset and severe form of moyamoya disease, patients with non-atherosclerotic quasi-moyamoya disease did not harbor the variant.20,21) The genetic background of moyamoya and quasi-moyamoya disease may be different.

Angiogenesis in POEMS syndrome

The biological effects of VEGF are angiogenesis and an increase in vessel permeability. Elevated levels of VEGF, interleukin (IL)-12, IL-1β, tumor necrosis factor (TNF)-α, and IL-6 have been reported in POEMS syndrome patients; VEGF is the cytokine that is consistently elevated and best correlated with disease activity.11) Although the pathogenesis of POEMS syndrome is not well understood, vascular hyper-permeability induced by VEGF is thought to be responsible

Fig. 1 Abdominal CT (A) Osteolytic lesion was detected in right pelvis. (B) Pelvic tumor became smaller and changed into osteosclerotic lesion.

Fig. 2 Pathological features of plasmacytoma (A) Diffuse proliferation of plasma cells (Hematoxylin and eosin 40×) (B) CD138 positivity (40×) (C) Lambda light-chain positivity (40×).
for its characteristic symptoms such as edema, pleural effusion, ascites, angioma, and organomegaly.\textsuperscript{22)\textcopyright}

The two thrombotic mechanisms in POEMS syndrome are hypercoagulability elicited by proinflammatory cytokines (IL-1\textbeta, TNF-\textalpha), thrombocytosis, polyclonabulias, hyperviscosity, hyperfibrinogemia, and angiogenesis of vasa vasorum accelerated by VEGF leading to intramural hemorrhage.\textsuperscript{2,5–7,9,11–13,15,23)\textcopyright}

Polyneuropathy is a required symptom for a diagnosis of POEMS. Elevated systemic levels of VEGF induce hypertrophy and proliferation of endothelial cells with secondary microangiopathy. The consequent reduction in the oxygen supply elicits a robust expression of HIF-1\textalpha (hypoxia inducible factor-1\textalpha) by all nerve constituents; a secondary increase in the local VEGF expression results in a self-perpetuating toxic gain of VEGF function.\textsuperscript{24)\textcopyright}

In our patient, fragile moyamoya vessels may have ruptured due to hemodynamic stress resulting in intracranial hemorrhage. Based on the above observations, we suggest that VEGF is one of the most important factors in the pathogenesis of POEMS syndrome.

**Similarity of moyamoya disease and POEMS syndrome**

Moyamoya vessels are thought of as the collateral circulation that develops to compensate for cerebral ischemia due to stenosis. Pathological findings on a sural nerve biopsy in a POEMS

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**Fig. 3** (A) MR angiography revealed narrowing of the proximal portion of the bilateral middle cerebral artery and the terminal portion of the internal carotid artery. (B) Brain CT scan demonstrating left putaminal hemorrhage. (C–E) MR angiography and cerebral angiography revealed occlusion of the proximal portion of the bilateral middle cerebral artery and narrowing at the terminal portion of the bilateral internal carotid artery. Note Moyamoya vessels. (F) Cerebral angiography demonstrated collateral circulation via leptomeningeal anastomoses in the posterior circulation. (G) SPECT (\textsuperscript{123I}-IMP) showed reduction of the CBF in the left frontoparietal cortex, left regional temporo-occipital cortex, and right cerebellum.
I. Yamaguchi et al.

### Table 1  Summary of previously reported patients with POEMS syndrome and cerebrovascular disease

| Reference | Number of cases | Age | Sex | Vascular structure |
|-----------|----------------|-----|-----|--------------------|
| Lesprit et al. 3 | 1 | 53 | F | Right ICA occlusion, left ICA stenosis |
| Forster et al. 4 | 1 | 59 | M | NA |
| Erro et al. 5 | 1 | 63 | F | Right ICA occlusion |
| Kang et al. 6 | 3 | 42 | M | NA |
| | | 48 | F | Proximal left MCA stenosis |
| | | 52 | F | Left ICA stenosis |
| Rössler et al. 7 | 1 | 32 | F | Right AI/M1 stenosis, left ICA occlusion |
| Garcia et al. 8 | 2 | 49 | M | Right M1 stenosis, left M1 occlusion |
| | | 50 | F | Bilateral ICA/M1/A1/PCA stenosis |
| Lee et al. 9 | 1 | 41 | M | Bilateral M1 occlusion and ICA stenosis |
| Huang et al. 10 | 1 | 42 | F | NA |
| Dupont et al. 11 | 9 | 46 (34–67) | F/M/F2 | Left M1 occlusion |
| | | 59 | Left M1 stenosis, left M1 occlusion |
| | | 60 | Right ICA occlusion |
| | | 62 | No major occlusion |
| | | 63 | Left ICA occlusion (dissection s/o) |
| | | 64 | NA |
| | | 65 | NA |
| | | 66 | NA |
| | | 67 | NA |
| Sommer et al. 12 | 1 | 54 | F | NA |
| Dacci et al. 13 | 1 | 49 | M | NA |
| Akyol et al. 14 | 1 | 47 | F | Bilateral M1 occlusion, left ICA stenosis |

A1: first anterior cerebral artery segment, ICA: internal carotid artery, M1: first MCA segment, MCA: middle cerebral artery, NA: not available, PCA: posterior cerebral artery.

The syndrome patient showed narrowing or occlusion of the vasculature. The findings may point to identical mechanisms underlying vessel occlusion. In response to vessel stenosis or occlusion due to hypoxia and a decreased vascular blood flow, angiogenic agents such as VEGF, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), transforming growth factor-β (TGF-β), and granulocyte-colony stimulating factor (G-CSF) are overexpressed in moyamoya disease. The presence of VEGF in the dura is an interesting finding that hints at the expansion of pathological mechanisms beyond the cerebral vasculature. In patients with atypical stroke presenting with multi-vessel stenotic lesions (moyamoya vessels) and polyneuropathy, POEMS syndrome must be ruled out. The observations made in our patient suggest the possible coexistence of POEMS syndrome and quasi-moyamoya disease. Stroke can precede the manifestation of the typical clinical features of POEMS syndrome. As it is a life-threatening condition, appropriate treatment must be delivered immediately.

### Conclusion

This is the first report of a patient with sudden-onset intracranial hemorrhage whose underlying morbidities were co-existing quasi-moyamoya disease and POEMS syndrome. In patients with atypical stroke who harbor multivessel stenotic lesions (moyamoya vessels) and manifest polyneuropathy, POEMS syndrome should be included in the differential diagnosis.

### Conflicts of Interest Disclosure

The authors declare no conflicts of interest.

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Coexistence of Quasi-moyamoya Disease and POEMS Syndrome

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