

Report

Vasculitic Neuropathy in a Patient with POEMS Syndrome

Miki SUZUKI, Megumi TAKEUCHI, Yumiko UCHIYAMA and Shinichiro UCHIYAMA

Department of Neurology, Tokyo Women's Medical University School of Medicine

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The rare paraneoplastic syndrome secondary to plasma cell dyscrasia referred to as POEMS syndrome is characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes. Levels of vascular endothelial growth factor (VEGF) are elevated in patients with POEMS syndrome and correlate with disease activity. Histopathological findings of nerve specimens usually reveal a mixture of segmental demyelination and axonal degeneration. We describe a patient with POEMS syndrome and obvious vasculitis in muscle and nerve biopsy specimens who had increased VEGF levels. POEMS syndrome accompanied by vasculitis has rarely been reported. We speculate that VEGF plays a pivotal role in the development of vasculitis in this disorder.

Key Words: POEMS syndrome, vasculitis, biopsy, vascular endothelial growth factor; VEGF

Introduction

POEMS syndrome is a rare multi-systemic disease that is generally associated with plasma cell dyscrasia and characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS). Also known as Crow-Fukase syndrome, POEMS is more common in Japan than elsewhere¹⁾. Vascular endothelial growth factor (VEGF) is considered to be responsible for various symptoms associated with this syndrome. Histopathology of the peripheral nerves of affected patients usually reveals segmental demyelination and secondary axonal degeneration. Vasculitis has rarely been identified in patients with POEMS syndrome. We herein describe a patient with POEMS syndrome accompanied by increased VEGF levels and vasculitis in muscle and nerve biopsy specimens.

Case Report

A 69-year-old Japanese male developed fever, diarrhea, and abdominal pain and was admitted to the Department of Gastroenterology 2 weeks thereafter. Within 10 days after admission, he developed bilateral leg pain and dysesthesia in the right first to third fingers followed by bilateral leg weakness and

dysesthesia in the left hand. He was transferred to the Department of Neurology. His medical history included hyperglycemia 3 months before admission and several years of hypertension.

A physical examination revealed clubbed fingers, glomeruloid angiomas on the abdominal skin, obvious bilateral lower extremity edema, hemangiomas on the chest and hypertrichosis. A neurological examination revealed muscular weakness of all four limbs that was predominant in the legs and more evident in the distal muscles, and absent deep-tendon reflexes in all extremities. Paresthesia and sensory loss of the glove-and-stockings type were present.

Increased plasma levels of creatinine, urea nitrogen and C-reactive protein (CRP) indicated renal dysfunction. Hematological assessments revealed mild leukocytosis and increased platelet counts, as well as elevated levels of plasma thrombin-antithrombin complex (TAT), D-dimer, fibrinogen degradation products (FDP), beta-thromboglobulin (β -TG) and platelet factor 4 (PF4). The hemoglobin A1c ratio was 8.2%. The patient was negative for autoantibodies such as rheumatoid factor, cryoglobulin, anti-double stranded DNA antibodies, and

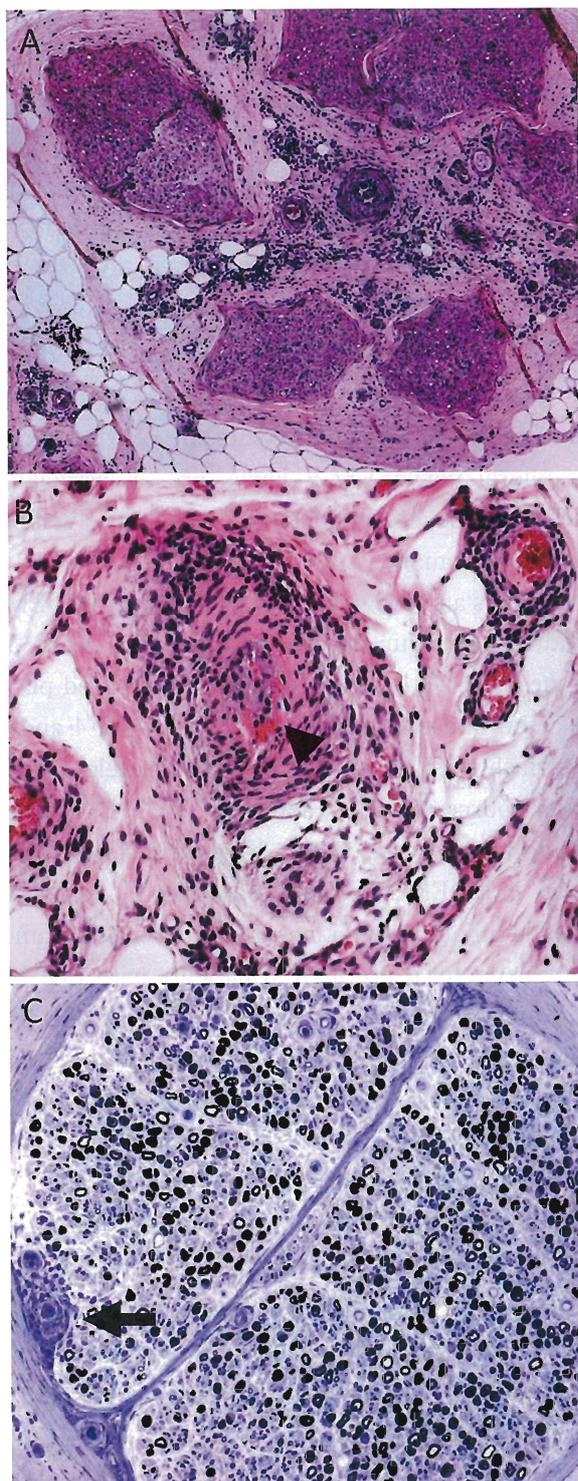


Fig. 1 Pathological features of biopsy specimens. Multifocal myelinated nerve fiber loss is evident within and between six fascicles of sural nerve, and perivascular and transmural inflammatory cell infiltrates are prominent in epineurial blood vessels (A, paraffin, H-E). Fibrinoid necrosis (arrow head), deranged wall and absent internal elastic membrane are also evident (B, paraffin, H-E). Myelinated nerve fibers showed acute axonal degeneration (C, Epon embedded specimen stained with toluidine blue). Arrow, perivascular cell infiltrates of endoneurial capillaries.

antineutrophil cytoplasmic autoantibodies (ANCA), but immunoelectrophoresis detected monoclonal IgG lambda type protein. The plasma VEGF level was 1.51 $\mu\text{g}/\text{mL}$. Interleukin 6 (IL-6) was also increased and Bence-Jones proteinuria was positive. Levels of cerebrospinal fluid protein were elevated. Motor and sensory nerve conduction studies revealed asymmetrical axonal changes. A CT scan of the chest revealed moderate pleural effusion and paraaortic lymphadenopathy. The findings of a scintigraphic bone scan were normal, thyroid function was suppressed, and a bone marrow biopsy revealed mild plasmacytosis (0.9%). These clinical and laboratory findings indicated POEMS syndrome.

A sural nerve biopsy revealed multifocal myelinated nerve fiber loss as well as prominent perivascular and transmural infiltrates of inflammatory lymphocytes, monocytes and macrophages into the epineurial blood vessels. Myelinated nerve fibers exhibited acute axonal degeneration. Vessel walls were disorganized, the lumina was obliterated and fibrinoid necrosis of the epineurial arteries was evident. In addition, perivascular cells had infiltrated the endoneurial capillaries (Fig. 1). A muscle biopsy revealed perivascular and endomysial inflammation.

We diagnosed POEMS syndrome accompanied by vasculitic neuropathy. Neither sclerotic bone lesions nor obvious plasmacytoma were evident. The patient was refractory to initial treatment with intravenous immunoglobulin (IVIg). Oral prednisolone then reduced the VEGF levels and improved the neuropathy, skin lesions, edema, fever and renal dysfunction.

Discussion

We described a patient with the characteristic clinical manifestations of POEMS syndrome associated with vasculitic neuropathy. A sural nerve biopsy showed axonal sensorimotor polyneuropathy and vasculitis. Steroid therapy improved all symptoms including the skin lesions, neuropathy, edema and renal dysfunction and decreased the plasma VEGF level. Thus, we speculated that vasculitic process played a role in all symptoms experienced by this patient, although tests for ANCA, anti-DNA

antibodies, antinuclear antibodies, rheumatoid factor, and cryoglobulin were negative. High-dose chemotherapy with a peripheral blood transplant has recently shown promise for treating POEMS syndrome². However, our patient had no overt plasma cell dyscrasia, and steroid therapy resulted in a good outcome.

Vasculitis is a very unusual component in POEMS syndrome. Shibata et al³ described overt necrotizing vasculitis in the adrenal gland at autopsy, and Sharabi et al⁴ described vasculitic skin lesions in a patient with this disorder. Vascular abnormalities might play an important role in POEMS' pathogenesis⁵⁻⁷. Evidence of vasculitis in peripheral nerves has rarely been reported⁸ but the pathophysiology of the neuropathy remains unclear. Vasculopathy of the small vessels in POEMS syndrome can be caused by several factors such as endothelial deposition of Ig or M-protein, coagulation abnormalities and increased levels of VEGF^{3,7,9}. An immunological effect of M-protein on a myelin antigen might cause the demyelinating neuropathy associated with POEMS¹⁰. Adams and Said¹¹ demonstrated endoneurial deposits of immunoglobulins in POEMS syndrome. Saida et al⁷ suggested that a barrier dysfunction at the endothelial level might play a role in the pathophysiology of this disease, and result in the edema of nerves and other organs. Watanabe et al⁹ speculated that VEGF affects the blood-nerve barrier by increasing microvascular hyperpermeability.

VEGF is a candidate pathogenic factor in POEMS syndrome, as it induces rapid and reversible increases in vascular permeability, it is a growth factor for endothelial cells, and it is considered important in angiogenesis and microvascular hyperpermeability¹². This growth factor is associated with many types of pathological angiogenesis, and it is up-regulated under conditions of perfusion insufficiency and increased metabolic demand, such as that associated with rheumatoid arthritis, Kawasaki disease, solid tumors, ischemic cardiac muscle and electrically stimulated skeletal muscle¹³. One study also found that VEGF is overexpressed in vasculitic lesions in biopsied sural nerves, and that plasma

VEGF levels are increased in dermatomyositis with peripheral neuropathy¹³. Sakai et al indicated that increased plasma VEGF levels could be useful as a diagnostic marker of vasculitic neuropathy and for monitoring therapeutic effects¹⁴. Thus, vascular abnormalities are associated with VEGF in POEMS syndrome. Scarlato et al reported that serum VEGF concentrations correlate with the severity of POEMS syndrome and suggested that VEGF might be one cause of this disease¹⁵. They also demonstrated that high serum VEGF, low serum EPO and high peripheral nerve VEGF levels are all associated with more severe endoneurial vessel involvement and nerve damage.

Platelets and coagulation are activated in POEMS syndrome^{9,16}. Our patient had elevated TAT, D-dimer and FDP levels as well as an increased platelet count and elevated plasma levels of PF4 and β -TG. Hashiguchi et al¹⁷ showed that platelets are a major source of VEGF, and that VEGF is released during platelet aggregation by physiological stimulation in POEMS syndrome. Serum levels of the proinflammatory cytokines IL-1 β , IL-6 and tumor necrosis factor- α are high in patients with POEMS syndrome⁹. Our patient had high IL-6 levels. We considered that the combined effects of VEGF and cytokines have specific functions in the various clinical manifestations of POEMS syndrome.

In conclusion, we described a patient with POEMS syndrome accompanied by rare vasculitis. VEGF might play a pivotal role in the development of vasculitic processes associated with POEMS. Steroid therapy is effective in this context for decreasing VEGF levels and improving the symptoms of POEMS syndrome.

The authors have no conflicts of interest to declare in association with this study.

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血管炎性ニューロパチーを呈した POEMS 症候群の 1 例

東京女子医科大学医学部神経内科学

スズキ ミキ タケウチ メグミ ウチヤマ ユ ミ コ ウチヤマシンイチロウ
鈴木 美紀・竹内 恵・内山由美子・内山真一郎

POEMS 症候群は比較的稀な疾患で、形質細胞異常症による傍腫瘍症候群の一つである。多発ニューロパチー、臓器腫大、内分泌障害、M 蛋白血症、色素沈着、剛毛などの皮膚症状を伴い、これらの頭文字をとって POEMS 症候群と呼ばれる。血清 VEGF (vascular endothelial growth factor) 高値が病態に関与するとされる。病理学的には末梢神経に節性脱髄と軸索変性の混在を示す。今回我々は、神経生検で明らかな血管炎性変化を伴った稀な POEMS 症候群の 1 例を経験したので考察を加えて報告する。本疾患では VEGF と血管炎の発症には関連があると考えられる。