LETTER TO THE EDITOR

To The Editor

Systemic Sclerosis Precedes POEMS Syndrome

Keywords: POEMS syndrome, Systemic scleroderma, Epilepsy, Neuropathy, Stroke

POEMS syndrome is a multisystem disorder characterized by polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes. Because skin manifestations, especially skin thickening and hyperpigmentation, are sometimes indistinguishable from what we see in patients with systemic sclerosis (SSc), these appearances have been referred to as scleroderma-like skin changes.[1] Besides these similarities in cutaneous appearances, abnormal activation and differentiation of B cells and generation of antibody-producing plasma cells played a role in both disorders, indicating the existence of a common pathogenic mechanism. It is, however, quite rare that SSc-specific antibodies are positive in POEMS syndrome. Here, we report a patient who was initially diagnosed as SSc due to skin thickening of both hands and Raynaud's phenomenon with anti-centromere antibody, an antibody specific for SSc, eventually developed into the POEMS syndrome.

At the age of 66, a focal seizure occurred in the right side of face and right hand. Her brain magnetic resonance imaging (MRI) showed a gadolinium-enhancing lesion in the left frontal lobe without apparent mass effect (Figure 1B). Pathological examination of a brain-biopsy specimen revealed a normal brain tissue (Figure 1E–G). The antiepileptic drug was effective for preventing recurrence of seizures. A year after, pedal edema in lower extremities, Raynaud's phenomenon, and scleroderma in both hands appeared. She was neurologically free. Blood examination detected high titers of antinuclear antibody and anti-centromere antibody (×280), leading to the diagnosis of SSc. Four months later, dysesthesia in soles presented and gradually progressed, which brought her to our hospital. Sausage-like fingers and hyperpigmentation of both hands and feet were observed (Figure 1A). Pitting edema and hairiness on both lower legs were also present. Retinal examination did not reveal any abnormalities. Neurological examination revealed distal dominant muscle weakness and sensory loss and decreased deep tendon reflexes in four extremities. Blood examination showed renal dysfunction (BUN 23 mg/dL, Cre 0.9 mg/dL) and an elevated pro-BNP value of 1066 pg/mL (normal range 0.0–125.0 pg/mL). The immunoglobulin levels were within a normal range, however, an IgA-λ monoclonal protein was detected by immunoelectrophoresis (IEP) and flow cytometry. In addition, serum vascular endothelial growth factor (VEGF) level was raised to 4560 pg/mL (normal range ≦ 38.3 pg/mL). Cerebrospinal fluid (CSF) analysis showed an elevated protein level of 106 mg/dL (normal range < 45 mg/dL) with normal cell count. The abnormal lesion in the left frontal lobe disappeared on the brain MRI (Figure 1C), suggesting the possibility of a transient ischemic attack and/or a focal epilepsy causing the initial MRI lesion. However, 24-hour Holter electrocardiography; cardiac, carotid, and leg vein ultrasound failed to detect risk factors for embolic strokes. Chest and abdominal computed tomography (CT) showed hepatosplenomegaly and pericardial fluid (Figure 1D). Whole-body CT and X-ray did not show any osteosclerosis. The results of nerve conduction study (NCS) showed diffuse reduction in sensory and motor nerve conduction velocities in median, ulnar, tibial, and peroneal nerves with prolonged F wave latencies, suggesting sensory and motor demyelinating polyneuropathy (Figure 1I and Table 1). Electromyography (EMG) showed acute denervation in biceps brachii. No abnormalities were observed in electroencephalogram. A bone marrow biopsy revealed plasma cell aggregation and Russell bodies in a small number of plasma cells. Sural nerve biopsy revealed mild axonal loss without demyelination (Figure 1H). No amyloid deposits were found in the muscle, nerve, or kidney. While the diagnosis of SSc had already been established, these results were satisfied with the criteria for definite POEMS syndrome.[2] While the results for NCS also met the electrodiagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in the European Federation of Neurological Societies/Peripheral Nerve Society guideline, POEMS syndrome is listed in the clinical exclusion criteria.[3] The treatment with thalidomide attenuated her edema and increased nerve action potentials.

To further characterize her anti-centromere antibody, we conducted anti-CENP B ELISA using different secondary antibodies, including anti-human IgG H&L (for detecting all immunoglobulins), anti-human IgG specific for Fc (for detecting only IgG), and anti-human IgA (for detecting only IgA).[4] While her anti-centromere antibody did not react with anti-human IgG specific for Fc, it reacted with both anti-human H&L and anti-human IgA, revealing her anti-centromere antibody to be IgA class, which raised the possibility of the monoclonal IgA itself to function as an anti-centromere antibody. This result indicates that her aberrant plasma cells lead to both POEMS syndrome and SSc.

This case illustrates the concomitant presentation of SSc and POEMS syndrome after the onset of symptomatic epilepsy, probably due to a transient ischemia. Stroke is not common, but it is one of the important complications associated with POEMS syndrome. The previous report indicated that the 5-year risk of stroke in POEMS syndrome was 13.4%.[5] Most of them had multiple lesions. The predicted etiology is thrombocytosis, hyperfibibrinogemia, or cerebral vasculopathy caused by elevated IL-6, IL-1, or VEGF. Because her symptoms and brain MRI lesions were both transient and brain-biopsy specimens revealed a normal brain tissue, cerebral embolism and early seizure are assumed to be her initial symptoms of POEMS syndrome. A lack of general risk factors for cardiovascular disease, hypercoagulation, and vasculitis supports this assumption.

POEMS syndrome is a paraneoplastic disorder caused by plasma cell dyscrasia. It was originally described in a patient with multiple myeloma (MM), which is a cancer of plasma cells.[6] Later, POEMS syndrome was recognized as a distinct disorder, showing a variety of clinical manifestations, some of which were partially explained by vascular permeability caused by elevated serum VEGF levels, but the precise pathogenic mechanism remains to be elucidated.[7]

SSc, one of the major autoimmune diseases, is based on the dysregulation of plasma cells, and therefore, a similar pathogenic

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Table 1: Results of the NCS

NCS	Nerve	Distal Latency (ms)	Amplitude (motor: mV, sensory: μV)	Conduction Velocity (m/s)	F-wave
			S1	S1–S2	Latency (ms)
Motor	Rt. median	4.65	6.64	37.4	40.2
	Rt. ulnar	3.54	3.93	34.5	53.4
	Rt. tibial	5.50	1.86	29.0	97.5
	Rt. peroneal	U/D	U/D	U/D	U/D
Sensory	Rt. median	3.40	7.30	41.2	
	Rt. ulnar	3.44	6.00	40.7	
	Rt. sural	U/D	U/D	U/D	

Median: S1: wrist, S2: elbow. Ulnar: S1: wrist, S2: below elbow. Tibial: S1: ankle, S2: popliteal. Peroneal: S1; ankle, S2; head of fibula.
U/D: undetectable.
Base-to-peak amplitude of the compound muscle action potential and sensory nerve action potential were measured.

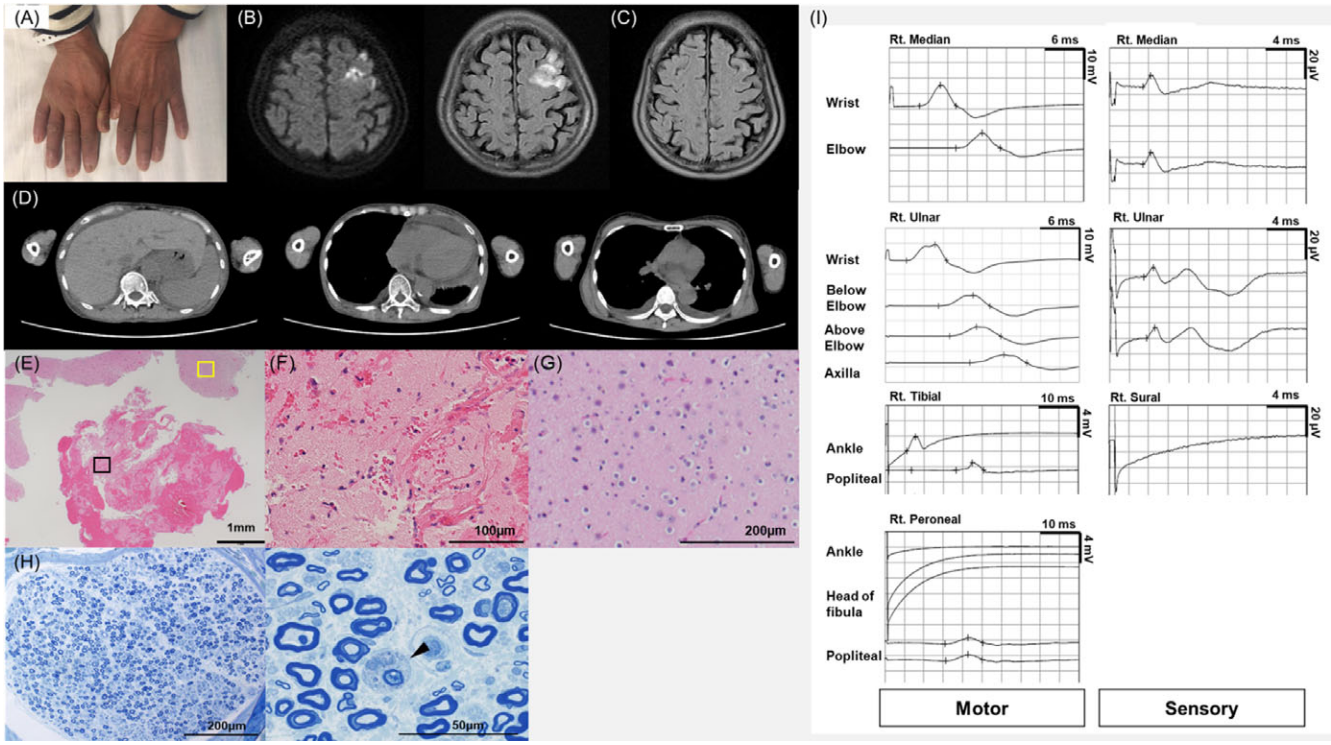

Figure 1: *Hands' appearance, brain MRI, CT of the trunk, NCS, and sural nerve biopsy. (A) Fingers were swollen like sausages (Sausage-like fingers) and hands were hyperpigmented. (B) Brain MRI was performed when the seizure occurred; diffusion-weighted image (DWI) and fluid-attenuated inversion recovery (FLAIR) revealed an abnormal high-intensity area (HIA) at the left frontal lobe (left side; DWI, right side; FLAIR). (C) Brain MRI on admission at the Juntendo University Hospital; FLAIR imaging barely showed an HIA. (D) Chest and abdominal CT showed hepatosplenomegaly and pericardial fluid. (E–G) A brain biopsy specimen from the left frontal lobe revealed normal brain tissue with an H&E stain. (F) Magnified view of the black rectangular area in (E). (G) Magnified view of the yellow rectangular area in (E). (H) Sural nerve biopsy revealed mild axonal loss (left) and degenerating axon infiltrated by macrophage (arrowhead) (right). (I) NCS of the right median, ulnar, tibial, peroneal, and sural nerves demonstrated diffuse reduction of nerve conduction velocity.*

mechanism between SSc and MM is suggested and further indicated by the high incidence of MM in patients with SSc – about 2.4 times higher than in normal population.[8] In contrast, concomitant autoimmune disorders have rarely been reported in patients with POEMS syndrome. Skin lesions of both disorders are similar in appearance, though the involvement of sweat glands and collagen is useful for differential diagnosis.[9] More recently, POEMS syndrome is associated with monoclonal plasma cells that exclusively use only two immunoglobulin λ light-chain variable region (IGLV) genes, IGLV 1-40 or IGLV

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1-44, suggesting that the only strictly monoclonal plasma cells can induce POEMS syndrome.[10] In contrast, widespread genetic heterogeneity is frequently observed in plasma cells from MM or monoclonal gammopathy of undetermined significance (MGUS).[11] This strict monoclonality might result in rare complications of autoimmune disorders in the POEMS syndrome. Indeed, POEMS syndrome often presents scleroderma-like skin changes, but these patients have never become seropositive for SSc-specific antibodies. The current case is unique in that dysregulating plasma cells produced monoclonal proliferation of IgA-λ, which caused POEMS syndrome, but also recognized the centromere, a specialized protein complex on chromosome. Because anti-centromere antibody is specifically positive for SSc, the patient had comorbid seropositive SSc.

In sum, we have experienced a patient who initially presented a partial seizure caused by a brain ischemic damage, then progressed seropositive SSc and finally developed into the POEMS syndrome. Our examination indicated that all clinical symptoms may be explained by the monoclonal IgA-λ produced from the aberrant plasma cells.

Consent

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images.

Disclosures

The authors declare that they have no conflict of interest.

Statement of Authorship

YY drafted, TT revised, and NH reviewed the manuscript. YY, YT, TT, and SS treated the patient. DT and MT assisted histological analysis. TNT assisted nerve conduction study. MS and NK provided useful suggestions.

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