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【 CASE REPORT 】

Severe Mononeuritis Multiplex due to Rheumatoid Vasculitis in Rheumatoid Arthritis in Sustained Clinical Remission for Decades

Masanobu Tanemoto[1], Shin Hisahara[1], Bungo Hirose[1], Kazuna Ikeda[1], Takashi Matsushita[1], Shuichiro Suzuki[1], Tatsuo Manabe[1], Tomihiro Imai[1,2] and Shun Shimohama[1]

Abstract:
Rheumatoid vasculitis (RV) usually occurs in patients with refractory rheumatoid arthritis (RA). An 80-year-old woman was transferred to our hospital because of muscle weakness and paresthesia in all 4 limbs. She had been diagnosed with RA 30 years ago and achieved sustained clinical remission. At presentation, polyarthritis and drop foot were observed, and rheumatoid factor was prominently elevated. A peripheral nerve conduction test revealed mononeuritis multiplex in her limbs. We suspected that RV had developed rapidly despite RA having been stable for many years and started immunosuppression therapy with steroids combined with azathioprine. The treatment prevented worsening of muscle weakness and paresthesia.

Key words: rheumatoid vasculitis, malignant rheumatoid arthritis, mononeuritis multiplex, rheumatoid arthritis

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Introduction

Mononeuritis multiplex is caused by various pathological conditions, although the main cause is vasculitis (1). Rheumatoid vasculitis (RV) occurs in some patients who have had rheumatoid arthritis (RA) over a long period of time, and most patients have refractory disease, such as progressive joint destruction (2). It is rare for RV to develop in patients with RA who have achieved sustained clinical remission over a long period. In such cases, the diagnosis and treatment tend to be delayed.

We herein report a case of severe vasculitic mononeuritis multiplex in RA with an atypical clinical course of RV.

Case Report

An 80-year-old Japanese woman was transferred to our hospital because of muscle weakness and paresthesia of all 4 limbs. Thirty years ago, she had developed painful swelling in the left hand joints and been diagnosed with RA. She also had a history of diverticulosis of the colon but no history of allergic diseases, such as bronchial asthma.

She had been followed using only non-steroidal anti-inflammatory drugs (NSAIDs) because the disease activity was very mild. Seven months before her presentation at the previous hospital, the C-reactive protein (CRP) and rheumatoid factor (RF) levels had been slightly elevated at a periodic blood examination performed at the clinic. Three months before her transfer, she passed a large amount of melena, necessitating blood transfusion, but the bleeding site could not be identified. Two months later, bilateral lower limb joint pain and myalgia appeared. About 10 days before admission to the previous hospital, she had a fever of maximum 38℃ and was not able to open the top of a plastic bottle.

At admission to the previous hospital, she had been unable to stand alone, and painful swelling of her limbs had been observed. Hypoesthesia of both soles and right drop foot were seen. CRP levels were elevated, and the erythro-

[1]Department of Neurology, Sapporo Medical University, School of Medicine, Japan and [2]Sapporo Medical University, School of Health Sciences, Japan
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Correspondence to Dr. Shin Hisahara, hisahara@sapmed.ac.jp

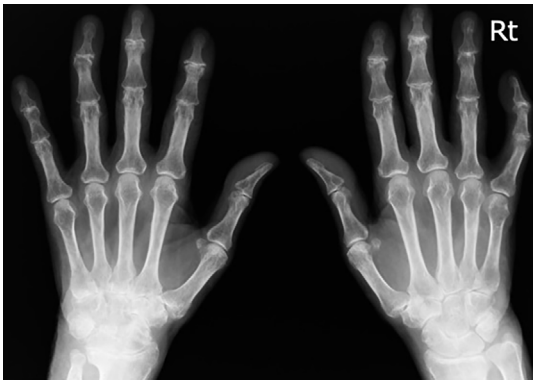

Figure 1. X-ray imaging of the hands. The joint space was symmetrically narrow mildly, but there was no joint destruction.

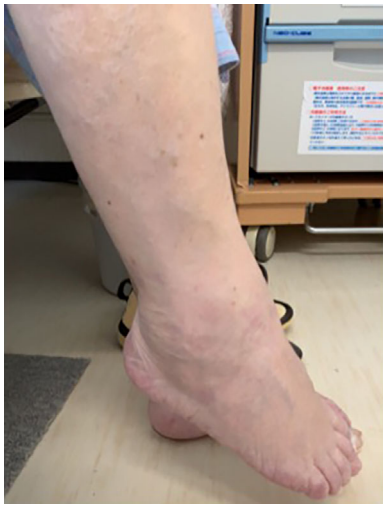

Figure 2. Bilateral drop foot observed at admission. The patient was instructed to dorsiflex her right leg.

cyte sedimentation rate (ESR) had increased to 125 mm/h. However, while RF and anti-citrullinated protein antibody (ACPA) were positive, several other auto-antibodies were negative. RF was elevated markedly to 682 IU/mL. Although the previous physician suspected infectious disease or a malignant tumor, neither were evident. Vasculitis was also suspected clinically, and oral prednisolone (PSL) at 50 mg/day and a first course of methylprednisolone (mPSL) pulse therapy (1 g/day, 3 days) were administered, but left drop foot developed. The patient was then transferred to our hospital for the further investigation of the cause of vasculitis.

The patient's height was 151 cm. She weighed 49.4 kg and had lost 8 kg in 3 months. Her body temperature was 36.7℃, blood pressure was 131/99 mmHg, and heart rate was 92 beats per minute. Her respiratory rate was 13 breaths per minute, and percutaneous oxygen saturation (SpO_2) was 95% on room air. No enlarged lymph nodes in the neck, axilla, or groin were detected. No edema or purpura were seen in the limbs. There was mild pain in the proximal interphalangeal joints of her fingers, but no swelling or redness was noted in any joints. X-ray imaging of the hands showed mild symmetrical joint space narrowing, but there was no joint destruction (Fig. 1). Her consciousness was clear, and her cognitive function was normal. Cranial nerve impairment was not detected. The grip strength decreased to 9 kg in the right hand and 5 kg in the left hand. A manual muscle test (MMT) showed decreases in the grade in her limbs (right/left) as follows: biceps 4/4, flexor carpi radialis 5/4, anterior tibialis 0/0, and gastrocnemius 3/2. Bilateral foot drop was observed (Fig. 2). She felt severe superficial sensory and deep sensory disturbance in her lower limbs, including the soles and dorsum of her foot, bilaterally but predominantly on the right side. All deep tendon reflexes were diminished. She was unable to stand alone. Her autonomic nervous function was normal.

The results of her blood examination are shown in Table 1. Inflammatory response parameters, such as the white blood cell count, CRP, and ESR, were elevated, but the eosinophil count was normal. The prothrombin time and activated partial thromboplastin time were normal, but the D-dimer level was elevated to 6.8 μg/mL. The high glucose level and HbA1c suggested impaired glucose tolerance. RF and ACPA were high, but other auto-antibodies were negative. RF classified as IgG (IgG-RF) and immune complex C1q (IC-C1q) were mildly elevated.

On day 1, a peripheral nerve conduction test revealed a decline in the compound muscle action potential (CMAP) in the bilateral median and ulnar nerves compared to the reference value (3). However, the sensory nerve action potential (SNAP) was declined only in the bilateral median nerves. Neither CMAP nor SNAP was evoked in the bilateral fibular, tibial, or sural nerves (Fig. 3, Table 2). Magnetic resonance imaging (MRI) performed by her previous doctor showed high-intensity lesions in the right ventricular trigonum and parietal lobe on diffusion-weighted image (DWI), indicating a new cerebral infarction (Fig. 4). Magnetic resonance angiography (MRA) showed narrowing of the left middle cerebral artery (MCA) and right posterior cerebral artery (PCA). We also performed MRI on day 1 and found no exacerbation of cerebral infarction. An electrocardiogram showed paroxysmal atrial fibrillation. An echocardiogram showed no evidence of valve vegetation or thrombi. We also performed a Holter electrocardiogram, which showed frequent premature atrial contraction and paroxysmal atrial fibrillation twice.

Mononeuritis multiplex was suspected because motor and sensory paralysis in the distal limbs had progressed sporadically, and this diagnosis was supported by the results of the peripheral nerve conduction test. The clinical course and test results strongly suggested vasculitis, although there was no purpura. A skin biopsy was performed from the right sole. No pathological findings, including prominent vasculitis, were observed. Therefore, a nerve biopsy or muscle biopsy was considered necessary for the diagnosis. However, given the risk of wound infection during administration of high-dose steroids at her age, we only performed a skin biopsy.

Table 1. Laboratory Data on Admission.

Complete Blood Count		Biochemistry Test		Immunoserological Test	
WBC	17,400 /μL	Alb	2.4 g/dL	CRP	3.57 mg/dL
Hb	9.6 g/dL	CK	12 U/L	IgG	943 mg/dL
Plt	426,000 /μL	AST	14 U/L	IgA	226 mg/dL
Coagulation		ALT	12 U/L	IgM	259 mg/dL
PT INR	1.06	LD	139 U/L	C3	81 mg/dL
APTT	28.2 sec	ALP	411 U/L	C4	15 mg/dL
D-dimer	6.8 μg/mL	γGTP	98 U/L	C1q	3.1 μg/mL
ESR	31 mm/h	Cr	0.54 mg/dL	ANA	1:40
Infectious Disease Test		BUN	20 mg/dL	RF	466 IU/mL
HBsAb	positive	Na	133 mEq/L	IgG-RF	3.1 (index)
HBcAb	positive	Cl	93 mEq/L	ACPA	25.5 U/mL
HBV DNA	not detected	K	3.4 mEq/L	MPO-ANCA	negative
anti HIVAb	(-)	Thiamine	42 ng/mL	PR3-ANCA	negative
anti HTLV1Ab	(-)	Cyanocobalamin	4,694 pg/mL	Anti-SS-A-Ab	negative
Tumor Marker		Folate	1.95 ng/mL	Anti-SS-B-Ab	negative
IL2-R	851 U/mL	Ferritin	283 ng/mL	ds-DNA IgG	negative
CEA	4.3 ng/mL	ACE	2.1 U/mL	Anti Sm-Ab	negative
CA125	38 U/mL	HbA1c	7.6 %	Anti RNP-Ab	negative
CA19-9	7.6 U/mL	Glucose	247 mg/dL	Cryoglobulin	negative

WBC: white blood cell count, Hb: hemoglobin, Plt: platelet, PT INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time , ESR: erythrocyte sedimentation ratio, Ab: antibody, sIL2-R: serum interleukin 2 receptor, Alb: albumin, CK: creatine kinase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LD: lactic dehydrogenase, ALP: alkaline phosphatase, γGTP: γ-glutamyl transpeptidase, Cr: creatinine, ACE: angiotensin converting enzyme, CRP: C-reactive protein, Ig: immunoglobulin, ANA: anti nuclear antibodies, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibody, MPO: myeloperoxidase, ANCA: anti-neutrophil cytoplasmic antibody, PR3: proteinase-3, SS: Sjögren syndrome, RNP: ribonucleoprotein

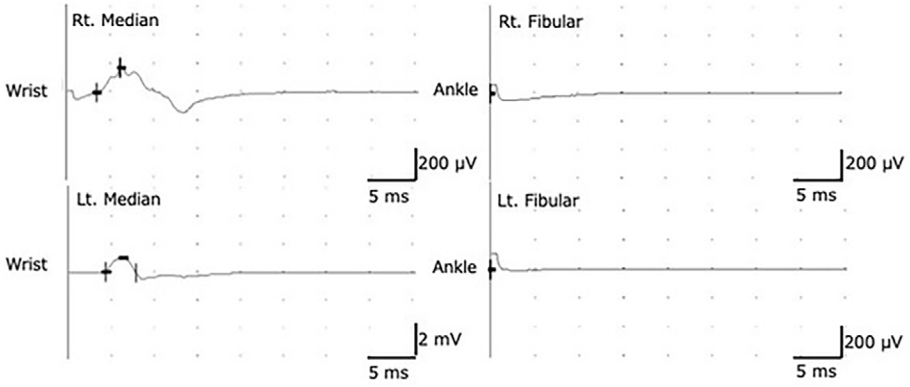

Figure 3. Motor nerve conduction study of the median nerve and fibular nerve. Compound muscle action potential (CMAP) was not evoked in the fibular nerve and declined in the median nerve predominantly on the right side.

Based on the findings of worsened mononeuritis multiplex with an elevated inflammatory response, high RF, and the presence of IgG-RF and IC-C1q, we suspected that the patient had RV.

Oral PSL 50 mg/day was continued from day 1, and a second course of mPSL pulse therapy (1 g/day, 3 days) was administered on days 3 to 5. She had already taken clopidogrel for three years because she had a history of transient ischemic attack and her left middle cerebral artery was narrow. Since paroxysmal atrial fibrillation was considered to be an indication for anti-coagulation therapy, dabigatran etexilate was administered in addition to clopidogrel. We prescribed rehabilitation, such as ambulation training and skilled motor activities. The weakness in the limbs did not worsen, and the areas of superficial sensory disturbance did not broaden. Her CRP and RF values gradually declined and became negative (Fig. 5). Oral PSL was gradually decreased from day 20, while azathioprine (AZP) 50 mg/day was started. Although no improvement in her muscular strength or sensory disturbance in the lower limbs was observed, slight improvement in the muscular strength in the upper limbs was obtained. Continued occupational therapy enabled her to open the top of a plastic bottle and dress herself. On day 43, the patient was transferred to her previous hospital

Table 2. **Results of Peripheral Nerve Conduction Test.**

Mortor						
	DL (ms)	RV	Amp (mV)	RV	CV (m/s)	RV
Rt. Median	3.4	3.49±0.34 (Wrist)	0.18	7.0±3.0 (Wrist)	50	57.7±4.9 (Wrist-Elbow)
Lt. Median	4.3		0.95		54	
Rt. Ulnar	2.6	2.59±0.39 (Wrist)	12	5.7±2.0 (Wrist)	53	58.7±5.1 (Wrist-Elbow)
Lt. Ulnar	2.8		3.2		49	
Rt. Tibial	NE	3.96±1.00 (Ankle)	NE	5.8±1.9 (Ankle)	NE	48.5±3.6 (Ankle-Pop)
Lt. Tibial						
Rt. Fibular	NE	3.77±0.86 (Ankle)	NE	5.1±2.3 (Ankle)	NE	48.3±3.9 (Ankle-Fibular He)
Lt. Fibular						
Sensory						
	DL (ms)	RV	Amp (μV)	RV	CV (m/s)	RV
Rt. Median	NE	2.84±0.34 (Wrist)	NE	38.5±15.6 (Wrist)	NE	58.8±5.8 (Finger-Wrist)
Lt. Median						
Rt. Ulnar	2.3	2.54±0.29 (Wrist)	28	35.0±14.7 (Wrist)	50	54.8±5.3 (Finger-Wrist)
Lt. Ulnar	2.2		15		51	
Rt. Sural	NE	2.8±0.3 (Lower Leg)	NE	17.2±6.7 (Lower Leg)	NE	51.1±5.9 (Ankle-Lower Leg)
Lt. Sural						
Rt. Fibular	NE	2.24±0.49 (Lower Leg)	NE	13.9±4.0 (Lower Leg)	NE	47.3±3.4 (Ankle-Lower Leg)
Lt. Fibular						

DL: distal latency, RV: reference value, Amp: amplitude, CV: conduction velocity, NE: not evoked, Pop: Popliteal fossa, Fibular He: Fibular Head

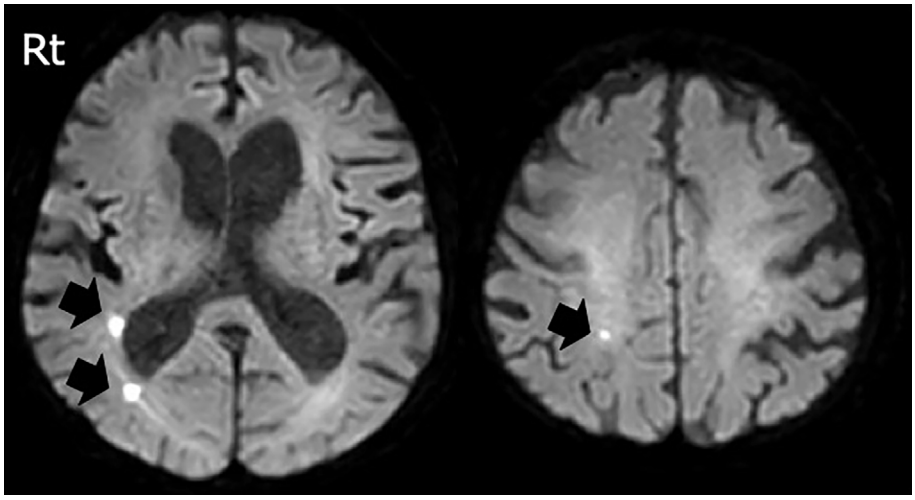

Figure 4. **Diffusion-weighted image of brain MRI on day 11. High-intensity areas are seen at the right ventricular trigonum and parietal lobe (arrows).**

to continue rehabilitation.

Discussion

We herein report a case of suspected RV that developed rapidly although RA as the underlying disease had been stable for many years. This case provides two clinical lessons. One is that RV may occur even though a patient with RA has been in sustained clinical remission for decades, and the other is that azathioprine combined with high-dose steroid therapy may be effective for vasculitis that occurs in aged patients.

RV is commonly a complication of RA with a prolonged course, and the disease duration is more than 13 years on average according to one report (4). In addition, many of the affected people have refractory RA, which causes joint destruction (2). MRA is RA with severe extraarticular symptoms, including vasculitis, and is almost synonymous with RV. The disease duration of RA in the present case was very long, and RA did not progress even though the patient was taking only NSAIDs. The clinical course therefore appeared to be stable. Two cases of RV with atypical clinical courses have been reported. One case presented with RV as a primary symptom, and the disease duration was two

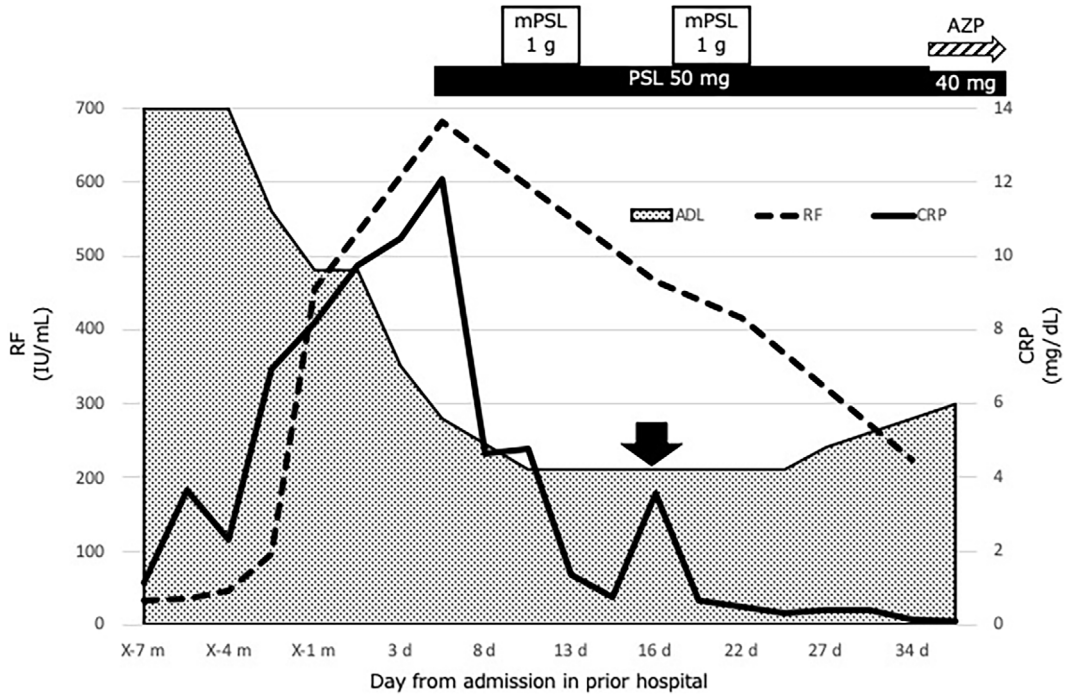

Figure 5. Clinical course. The patient's ADL deteriorated from the time diverticular bleeding occurred, and then muscle weakness followed. Elevations of RF and CRP were associated with fluctuation of the ADL. The patient was transferred to our hospital on day 16 (arrow). Immunosuppression therapy using PSL and AZP kept the weakness in the limbs from worsening, and slight improvement in the muscular strength in the upper limbs was obtained because of daily rehabilitation. ADL: activity of daily living, RF: rheumatoid factor, CRP: C-reactive protein, m: month, d: day, PSL: prednisolone, mPSL: methylprednisolone, AZP: azathioprine

months (5). The other case presented with ulcerative keratitis as the feature of RV without joint involvement (6). These cases show that RV may occur in new-onset RA or without joint involvement, and the disease duration or progression of RA may vary. We considered there to be an association between the development of RV and the long discontinuation of appropriate anti-rheumatic medications in our case. Disease-modifying anti-rheumatic drugs (DMARDs), especially methotrexate, are strongly recommended as a first-line agent of RA in the early stage and should not be discontinued even if patients achieve clinical remission (7, 8). Management of RA with DMARDs can decrease the incidence of RV (9), but DMARDs had not been used for decades in our case. There was a relatively high risk of the recurrence of RA, and some immune-mediated factors can trigger its recurrence as RV.

According to the RV diagnostic criteria of Scott and Bacon (1984) (10), RV should be considered when a patient has mononeuritis multiplex concomitant with RA. According to the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria (2010) for RA, "definite RA" is diagnosed based on the presence of polyarthritis, high RF and ACPA titers, a long disease duration, and high CRP and ESR values, as seen in this case (11). High RF values are seen at a high rate in RV (12). Although RF is generally classified as IgM in RA, IgG-RF is frequently found in RV (13). Hypocomplementemia may occur when IgG-RF forms an immune complex with the consumption of complement. Self-aggregated IgG has been reported to activate neutrophils and contribute to the pathogenesis of RV (14). High RF values and the presence of IgG-RF and IC-C1q observed in the present case were important for a diagnosis of RV (15).

Mononeuritis multiplex is characterized by peripheral neuropathy in at least two different nerve trunks and is frequently associated with vasculitis. MRI in our case showed findings indicating recent cerebral infarction, which can be caused by vasculitis. Not only inflammation of cerebral blood vessels but a hyper-coagulable condition due to systemic inflammation may have caused cerebral infarction in this case. In addition, RA is a risk factor of atrial fibrillation (16, 17). In the present case, the CRP and RF levels were increased seven months before presentation at the prior hospital, suggesting the timing of recurrence of RA or the onset of vasculitis (Fig. 5). The possibility that vasculitis contributed to gastrointestinal bleeding cannot be ruled out.

The medical history and examination findings did not suggest primary vasculitis such as anti-neutrophilic cytoplasmic antibody-associated vasculitis (AAV), sarcoidosis, cryoglobulinemia, infections, or drug-induced neuropathies. In case of suspected anti-neutrophil cytoplasmic antibody-negative vasculitis without organ damage other than damage to the nervous system, we have to consider non-systemic vasculitic neuropathy (NSVN), which causes disorders only

in the peripheral nerves. However, based on the exclusion criteria mentioned in the guideline by the Peripheral Nerve Society in 2010 (18), NSVN was not likely in our patient due to the presence of a central nervous lesion, marked elevation of ESR, and a definite diagnosis of ACPA-positive RA.

In the acute phase, RV requires strong immunosuppression therapy. The combined use of a high-dose steroid and cyclophosphamide or rituximab against systemic vasculitis is effective in general (10, 19, 20). However, we used AZP in combination with steroids since the patient was 80 years old, and adverse events due to immunosuppression were a concern. Although the effectiveness of AZP for RV is controversial (21), AZP combined with steroids has been used effectively as initial therapy for RV (22). In addition, there were no marked differences in the effectiveness or safety between AZP and cyclophosphamide when used as maintenance therapy for AAV (23). In our case, rapid treatment using a high-dose steroid and AZP successfully prevented worsening of the muscular strength and dexterity of the upper limbs.

Systemic RV may occur even if a patient with RA has been in sustained clinical remission for decades. Strong immunosuppression therapies are required when severe neuropathy coexists with vasculitis. Early treatment with high-dose steroids combined with AZP may be effective for vasculitis when considering the adverse effects of immunosuppression on aged patients. The functional outcome can be improved by preserving the residual function through a rapid diagnosis and treatment. Long-term follow-up of this patient is planned.

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

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