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A case of recurrent Mikulicz's disease with mononeuritis multiplex

ATSUSHI MIZUMA, MAIKO KOUCHI, CHIKAGE KIJIMA, SACHIKO YUTANI, TSUYOSHI UESUGI, EIICHIRO NAGATA, SHUNYA TAKIZAWA

Department of Neurology, Tokai University School of Medicine, Isehara, Japan

Abstract

We report an 82-year-old man with recurrence of Mikulicz's disease accompanied with mononeuritis multiplex. On admission, both upper eyelids, the salivary gland, the dorsum of the left hand and both legs were swollen. Neurological examination showed motor weakness of distal limbs (manual muscle testing 3/5) and decreased touch, pain and vibration sensation of the dorsum of the left hand and both legs. Deep tendon reflex in both legs was also decreased. We diagnosed Mikulicz's disease based on high serum immunoglobulin (Ig)G4 (630 mg/dl, 26.1% of total IgG) and lacrimal gland biopsy findings. Clinical symptoms and motor conduction study findings improved after steroid therapy. However, tapering of the steroid dose resulted in recurrence two years later. Steroid therapy is usually effective for IgG4-related neuropathy, and we found that an increase of steroid dose was effective to treat the recurrence. But, in general, a suitable maintenance dose of steroid in combination with an immunosuppressant may be necessary to prevent relapse.

Key words: *Mikulicz's disease, mononeuritis multiplex, IgG4, steroid therapy.*

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Introduction

Immunoglobulin (Ig)G4-related disease (IgG4RD) is proposed as a novel disease entity associated with polyclonal increase and infiltration of IgG4 [1-3]. Pathologically, IgG4 plasma cells account for more than 40% of total IgG plasma cells in patients [4]. Single or multiple organs may be affected, with various symptoms, such as pancreatitis and sclerosing cholangitis [5]. IgG4RD, which responds well to steroid therapy [6], is known to be associated with hypertrophic pachymeningitis and hypophysitis in the central nerve system [7, 8]. On the other hand, there are few reports of peripheral nerve palsy associated with IgG4RD [9] and neuropathological criteria for IgG4RD have not been established.

Mikulicz's disease (MD) is included in IgG4RD [10]. The main features of MD are high serum IgG4 and bilateral lacrimal/salivary persistent swelling [10]. A case of MD with eosinophilic granulomatosis with polyangitis (Churg-Strauss syndrome) was previously reported with coexistence of neuropathy due to allergic reaction [11]. On the other hand, a case of neuropathy with MD itself has not been reported, even if a lot of other IgG4RD were reported to coexist with MD.

The clinical course of IgG4RD is diverse. Exacerbation is often seen during tapering of the steroid dose [12], while spontaneous remission is seen in some cases [13]. Clinical outcomes of peripheral neuropathy are unclear, in contrast to other IgG4RDs, such as autoimmune pancreatitis (AIP) [14] and IgG4-related sclerosing cholangitis (IgG4-SC) [15].

Here, we report the clinical course of a case of MD with mononeuritis multiplex.

Case report

An 82-year-old Japanese man was admitted to our hospital with gait disturbance. He had previously been diagnosed with angina, atrial fibrillation, hypertension and diabetes mellitus (DM). He had experienced pain and swelling of the left hand and right toe a few days before admission. These symptoms were progressive and made it difficult for him to walk. Similar symptoms had appeared on the right upper and lower extremities one year before, and he was treated with an antibiotic at another hospital. However, the pain and swelling had not improved, and joint deformation remained.

On admission, his blood pressure, heart rate and temperature were 150/100 mmHg, 92 beats per minute, and 37.0°C. His consciousness state was alert. Both upper eyelids, the salivary gland, the dorsum of the left hand and both legs were swollen (Fig. 1A-1, 2). He also reported joint pain and showed a limited range of motion. Scratches were also seen on both dorsa of the feet. Neurologi-

Correspondence: Atsushi Mizuma, MD, PhD, Department of Neurology, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa, 259-1193, Japan, e-mail: a-mizuma@is.icc.u-tokai.ac.jp
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cal examination showed motor weakness of distal limbs (manual muscle testing 3/5) and decreased touch, pain and vibration sensation of the dorsum of the left hand and both legs. Deep tendon reflex in both legs was also decreased. Laboratory examinations revealed high inflammatory responses (white blood cell count 13 200/μl (neutrophils 72.2%, lymphocytes 16.7%, eosinophils 0.1%), C-reactive protein 14.37 mg/dl, elevated sedimentation rate 34 mm/h) and hyperuricemia (9.7 mg/dl). Liver function (aspartate transaminase, alanine transaminase, γ-glutamyltransferase, lactate dehydrogenase), renal function (blood urea nitrogen, creatinine), and amylase were within normal ranges. Glycometabolism (HbA_{1c} [5.7%]), thyroidal function (thyroid-stimulating hormone, free T4), creatine kinase, and gonadal hormones (testosterone [0.69 ng/ml])were also within normal ranges. High serum IgG (2417 mg/ml) and IgG4 (630 mg/dl, 26.1% of total IgG) were seen, although autoimmune antibodies were all negative (rheumatoid factor, anti-nuclear antibody, anti-cyclic citrullinated peptide antibody, anti-topoisomerase antibody, anti-centromere antibody, anti-SS-A antibody, anti-SS-B antibody, and anti-neutrophil cytoplasmic antibody). As for other serum laboratory examinations, immuno-electrophoresis showed a chronic inflammatory pattern and serum vascular endothelial growth factor was elevated (351 pg/ml). Cerebrospinal fluid (CSF) showed no elevation of protein or pleocytosis. Urinalysis was negative for protein, occult blood, glucose, and ketones. The cultivation test revealed *Staphylococcus aureus* in two blood cultures and no bacterium in CSF. No abnormal lesions were seen in brain and spine MRI. Wrist MRI revealed swelling of the synovium and myelin sheath with fluid accumulation on the left side. The electromyographic (EMG) study showed signs of mononeuritis multiplex (Table 1). In conduction studies, compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) were absent in the left median and ulnar nerves. In the right median and left lower extremities, CMAP amplitudes were reduced. Needle EMG showed neurogenic changes with the voluntary movement of the upper and lower extremities, and no denervation potential at rest. Enhanced computed tomography and gallium scintigraphy showed no inflammatory lesions or malignant tumors. Lymph node echography showed only reactive swellings. Lacrimal and salivary gland echography showed low echoic mass lesions, suggesting swelling of the glandular tissue. Based on this finding, a la-

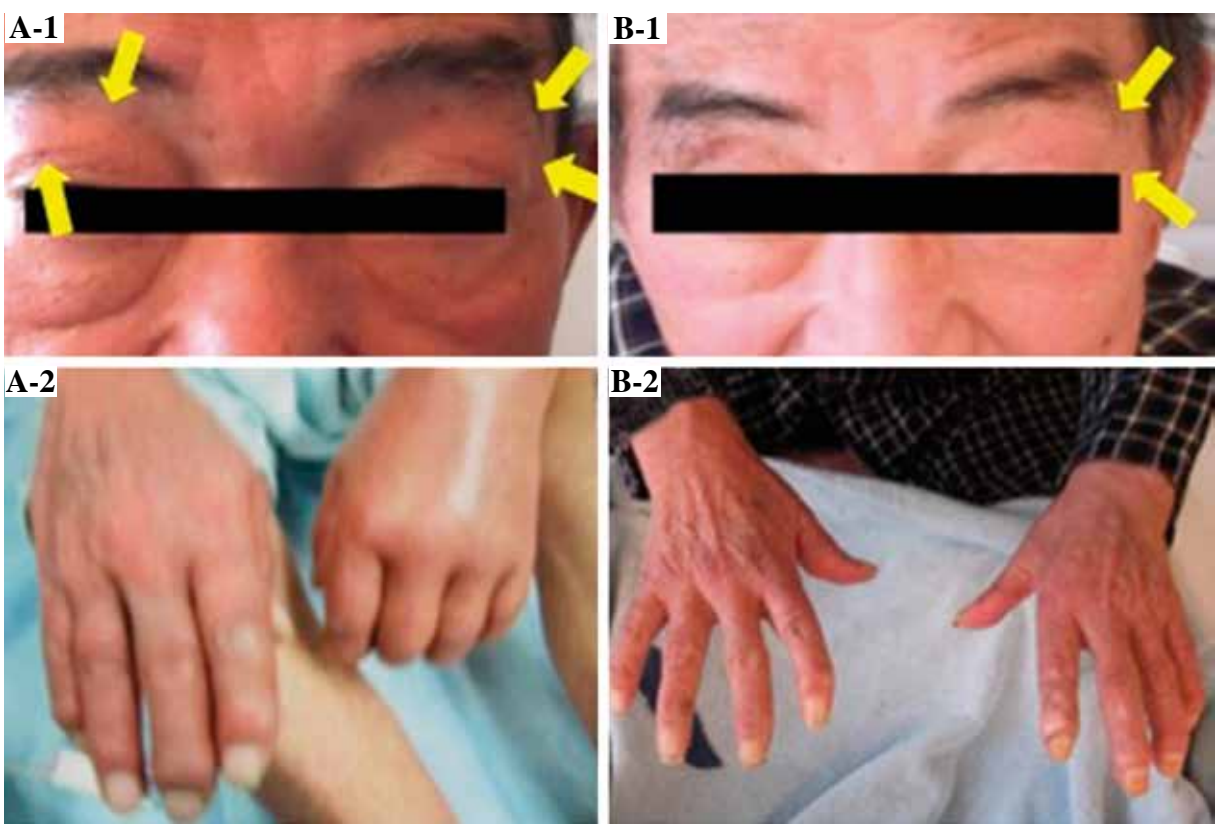

Fig. 1. A) On admission. Both upper eyelids (1) and the left dorsum of the hand (2) were swollen. Joint pain and limited range of motion were also present. **B**) After steroid therapy. Swelling of upper eyelid (1) and left dorsum of the hand (2) were improved. Joint pain had disappeared and range of motion was improved

Table 1. Nerve conduction study showed signs of mononeuritis multiplex. Compound muscle action potentials (CMAPs) and sensory nerve action potentials (SNAPs) were absent in the left median and left ulnar nerves, respectively

	Site	Latency (ms)	Amplitude (mV)	Nerve conduction velocity (m/s)
Motor conduction study	Left median	Not detected	Not detected	Not detected
	Right median	4.32	1.826	43.6
	Left ulnar	3.99	3.299	41.7
	Left tibial	4.59	3.928	31.5
	Left peroneal	Not detected	Not detected	Not detected
Sensory conduction study	Left ulnar	Not detected	Not detected	Not detected

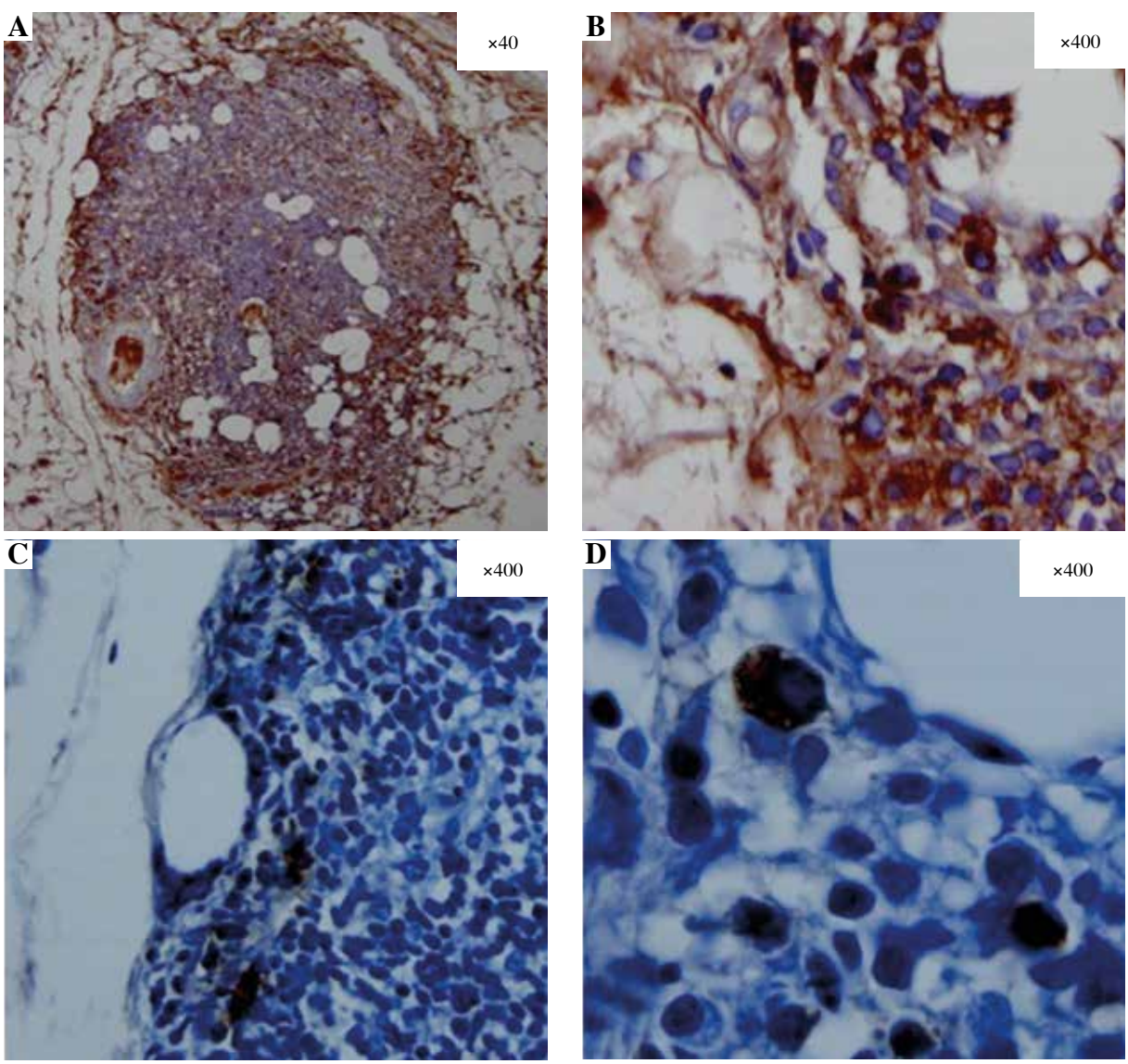

Fig. 2. A, B) Histopathologic examination of lacrimal gland biopsy revealed lymphoid follicles with germinal center. IgG-positive plasma cells on the lymphoid follicles were visualized by enzyme immunostaining. **C, D**) Enzyme immunostaining with an anti-IgG4 antibody revealed IgG-positive plasma cells, accounting for about a half of IgG4-positive cells on the lymphoid follicles

crimal gland biopsy was performed and showed lymphoid follicles with a germinal center. Enzyme immunostaining with anti-IgG4 antibody revealed IgG-positive plasma cells, of which about a half were IgG4-positive, on the lymphoid follicles (Fig. 2). Based on these results, Mikulicz's disease was diagnosed.

Clinical course

The clinical course is shown in Fig. 3. On admission, antibiotic therapy (cefazolin 2 g/day) was started to treat cellulitis, based on the results of blood culture. Considering comorbid polyarthritis with hyperuricemia, non-steroidal anti-inflammatory drugs (loxoprofen 180 mg/day) and benzbromarone were also started. Although his joint pain and swelling were reduced, the inflammatory reaction and neuropathy remained. The subsequent laboratory finding of high serum IgG4 and the lacrimal gland swelling were suggestive of IgG4RD. Nerve biopsy was not performed because of the remaining ankle swelling and pain. After lacrimal gland biopsy, he was diagnosed on MD and oral prednisolone was started at 40 mg/day, and the clinical symptoms (Fig. 1B-1, 2) and EMG findings improved. After discharge, the steroid dose was tapered because of his DM, reaching 3 mg/day after two years. However, at that time, lacrimal gland swelling reappeared, together with gait disturbance and elevation of serum IgG4. The steroid dose was increased to 10 mg/day and these symptoms improved.

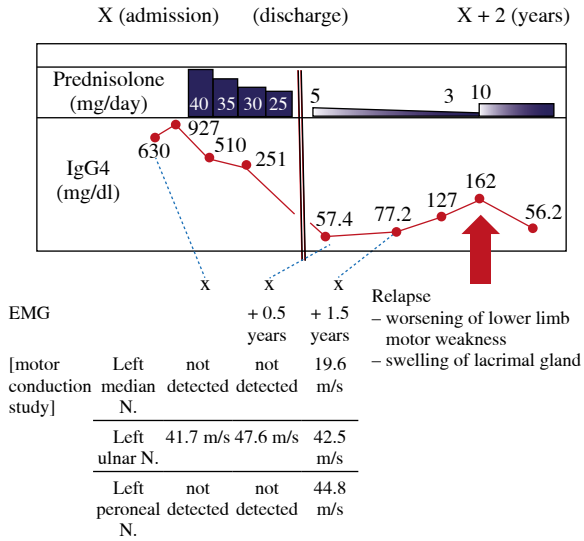

Fig. 3. On admission, antibiotic therapy (cefazolin 2 g/day) was started to treat cellulitis. Non-steroidal anti-inflammatory drugs (loxoprofen 180 mg/day) and benzbromarone were also started to treat polyarthritis with hyperuricemia. After a diagnosis of IgG4 related disorder, oral prednisolone was started at 40 mg/day. After starting oral prednisolone, the clinical symptoms and nerve conduction study findings improved. After discharge, the steroid dose was tapered. But at the time of reducing 3 mg/day of prednisolone dose, both lacrimal gland swelling and gait disturbance reappeared. Serum IgG4 was also elevated. The steroid dose was increased to 10 mg/day and these symptoms improved

Discussion

We present a case of recurrent mononeuritis multiplex with MD. This is of interest, because the frequency of peripheral neuropathy associated with IgG4RD remains unclear. Also, the recurrence of symptoms during tapering of steroid therapy suggests that addition of an immunosuppressant might be effective to prevent relapse.

Reported forms of IgG4RD include hypophysitis, pachymeningitis [7, 8], and cranial nerve neuropathy [16]. However, few cases with peripheral neuropathy in the distal extremities have been reported. Ohyama *et al*. [9] reported IgG4-related peripheral neuropathy diagnosed by sural nerve biopsy. Decrease of myelinated fibers, axonopathy, and infiltration of IgG4-positive plasma cells on the epineurium were pathologically recognized [9]. This report suggested that IgG4 related neuropathy was caused by vasculitis based on the pathological findings. As for the other etiology of IgG4-related neuropathy, Yamamoto *et al*. [11] reported a case of eosinophilic granulomatosis with polyangitis (Churg-Strauss syndrome) that met the diagnostic criteria for MD. This report suggested an association between IgG4-related neuropathy and vasculitis due to allergic reaction. The major difference in our case was occurrence of vasculitis due to MD rather than another allergic reaction, because there was no history of allergic disease and eosinophilia. Also, we needed to consider about the correlation with cellulitis from scratches and DM.

Aside from the neuropathy, we firstly considered that the limb swelling with joint pain was caused by cellulitis from scratches and started antibiotic therapy, even if we also considered it to be due to polyarthritis with hyperuricemia. After starting therapy, these symptoms were reduced, except for the motor weakness and sensory disturbance. Also, the limb swelling with joint pain was not in parallel with lacrimal gland swelling and neuropathy throughout the entire course. Therefore, we concluded that the cause of the limb swelling and joint pain was cellulitis. On the other hand, this cellulitis was not considered to be the cause of mononeuritis multiplex, but it was also considered to be important as an initial trigger of immunological inflammation. Secondly, we considered the correlation between mononeuritis multiplex and DM. Although the patient had a history of DM, other complications were not detected and the control of glycometabolism was good without using anti-diabetic drugs. Furthermore, this neuropathy was in parallel with serum IgG4 levels and the status

of MD (lacrimal gland swelling). From the above consideration, we finally made the diagnosis of mononeuritis multiplex associated with IgG4RD, due to the concurrence of IgG4 and Mikulicz's disease, even if sural nerve biopsy could not be performed because of ankle edema and pain.

Steroid maintenance therapy of AIP was reported to be effective in terms of remission rate and recurrence rate in a multicenter trial [14]. The international consensus recommendation is 0.6-1.0 mg/kg of oral prednisolone as remission induction therapy and 5 mg/day of prednisolone as maintenance therapy [17]. The recurrence rate without maintenance steroid therapy was reported to be about 50% [15], and maintenance steroid therapy is also recommended in other reports [12, 14]. On the other hand, the risk factors for recurrence appear to be different for each IgG4-targeted organ. AIP of pancreatic bile duct lesions, duration of high IgG4 [13, 14, 18] lacrimal gland sialadenitis [19] of juvenile onset and male sex were reported as risk factors for recurrence.

Recurrence has been reported at a rate of 15-56% on stopping steroid therapy or reducing it to 5-20 mg/day [13, 14, 20, 21]. It is suggested that an immunosuppressant (azathioprine, rituximab, or cyclosporine) should be added [22, 23] or the steroid dose should be increased at the time of recurrence [14]. In our case, recurrence was seen when the steroid dose was reduced because of the patient's DM. Increase of the steroid dose from 3 to 10 mg/day was effective to treat the relapse in our patient.

In conclusion, we reported a case of recurrent mononeuritis multiplex with MD. In this case, steroid therapy was effective for recurrent IgG4RD neuropathy, but in general, a suitable combination of a maintenance dose of steroid and an immunosuppressant may be desirable to prevent relapse of IgG4RD.

The authors declare no conflict of interest.

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