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[ CASE REPORT ]

**Immunoglobulin G4-related Disease Accompanied by Peripheral Neuropathy: A Report of Two Cases**

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**Abstract:**

Due to its rarity and the limited literature, the clinicopathological characteristics of peripheral nerve involvement in immunoglobulin G4 (IgG4)-related disease are unknown. We present two cases of IgG4-related disease, accompanied by peripheral neuropathy, presenting as unilateral ptosis (case 1) and sclerosing cholangitis (case 2), respectively. In both cases, sural nerve biopsy indicated vasculitis as the underlying pathophysiology; the peripheral neuropathy was refractory to corticosteroid therapy. In contrast to the previously proposed pathomechanism of IgG4-related neuropathy (direct lymphoplasmacytic infiltration), the pathological findings in our cases suggest that vasculitis occurs secondary to systemic autoimmune conditions.

**Key words:** case report, IgG4-related disease, systemic autoimmune disease, peripheral neuropathy, vasculitic neuropathy

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**Introduction**

Immunoglobulin G4 (IgG4)-related disease is a relatively new and emerging systemic autoimmune condition characterized by a distinctive histopathological appearance of lymphoplasmacytic infiltrates with abundant IgG4-positive plasma cells, storiform fibrosis, and obliterative phlebitis (1). The first case of apparent IgG4-related disease was reported by Jan Mikulicz-Radecki, in the late 19th century, as a case of lacrimal gland swelling followed by submandibular and parotid gland swelling (2). In the late 20th century, Kawaguchi et al. reported two cases in patients undergoing surgery for pancreatic carcinoma; the pathological findings were lymphoplasmacytic sclerosing pancreatitis with cholangitis (3). Hamano et al. reported serum IgG4 elevation in patients with sclerosing pancreatitis (4). In 2012, IgG4-related disease was described as a novel clinical entity (1).

Among the neurological involvements of IgG4-related disease, peripheral neuropathy is reported to be rare, occurring in <1% of patients with this disease (5). In 2013, Ohyama et al. reported the first case of IgG4-related peripheral neuropathy with direct lymphoplasmacytic infiltration in a patient with local IgG4-related skin lesions (6). However, no further cases of peripheral neuropathy caused by direct cellular infiltration have been reported since then. Thus, the clinicopathological characteristics of peripheral neuropathy in IgG4-related disease are unclear. We herein report two cases of IgG4-related disease with peripheral neuropathy.

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**Case Reports**

**Case 1**

An 81-year-old Japanese woman presented with a 6-month history of unilateral ptosis that appeared after a few
A laboratory examination revealed an elevated erythrocyte sedimentation rate (79 mm/h, reference: <17 mm/h) and hypergammaglobulinemia with beta-gamma (β-γ) bridging without a monoclonal band. The serum levels of immunoglobulin G (IgG) (2,754 mg/dL, reference: <1,700 mg/dL), IgG4 (1,310 mg/dL, reference: <117 mg/dL), and immunoglobulin E (764 U/mL, reference: <170 U/mL) were elevated. The anti-Ro/SSA antibody titer was 93 U/mL (reference: <7 U/mL) and the patient tested negative for anti-La/SSB antibodies. The level of anti-thyroglobulin was 1,697 U/mL (reference: <28 U/mL) and antithyroid peroxidase was 390 U/mL (reference: <16 U/mL). The patient tested negative for anti-neutrophil cytoplasmatic and anti-acetylcholine receptor antibodies. A nerve conduction study revealed an asymmetrical response in the right sural nerve (Table 1). Repetitive nerve stimulation showed normal neuromuscular transmission. Computed tomography (CT) showed retroperitoneal fibrosis, mediastinal and hilar lymphadenopathy, and enlargement of the thyroid gland and pancreas. Magnetic resonance imaging (MRI) revealed bilateral lacrimal gland swelling and enlargement of the left levator palpebrae superiors, indicating myositis or edema of the muscle (Fig. 1A; this improved after treatment, as shown in Fig. 1B).

Since the patient’s concerns were plantar dysesthesia as well as ptosis, she requested a nerve biopsy. The sural nerve biopsy revealed epineurial perivascular lymphocytic infiltration (Fig. 1C), vascular occlusion, loss of myelinated fibers, and myelin ovoids (Fig. 1D). To exclude malignancies or similar diseases (e.g., cancer, lymphoma, Sjögren’s syndrome, multicentric Castleman disease, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis), we performed lip, submandibular lymph node, and nasal mucosal biopsies. The lip (Fig. 1E-H) and submandibular lymph node biopsies revealed lymphoplasmacytic infiltration with an IgG4-/IgG-positive cell ratio of >70%. Finally, a diagnosis of IgG4-related disease with enlargement of the levator palpebrae superiors and peripheral neuropathy was made.

Considering the patient’s age, we treated her with oral prednisolone (10 mg/day; body weight, 45 kg). After one month of treatment, the ptosis and salivation, which she had thought to be a sign of aging, improved. The treatment response indicated that the dry mouth was due to IgG4-related sialadenitis. The plantar dysesthesia remained unchanged. Improvement of the levator palpebrae superiors and lacrimal enlargement were confirmed on MRI (Fig. 1B). Improvement of the pancreatic enlargement, lymphadenopathy, and retroperitoneal fibrosis were confirmed on CT. The dose of prednisolone had to be reduced to 5 mg/day due to the patient experiencing general fatigue, which improved without a relapse of other symptoms.

**Table 1. Nerve Conduction Study.**

| Age/sex | Case 1 | Case 2 | Controls |
|---------|--------|--------|----------|
|         | L      | R      | L        | R        | Mean | SD   |
| Median  |        |        |          |          |      |      |
| MCV (m/s) | 54     | 58     | 54       | 47       | 57.7 | 4.9  |
| DL (ms)  | 3.4    | 3.1    | 3.6      | 3.1      | 3.49 | 0.34 |
| CMAP (mV) | 7.1    | 6.0    | 9.7      | 9.0      | 7.0  | 3.0  |
| SCV (m/s) | 58     | 52     | 51       | 56       | 56.2 | 5.8  |
| SNAP (μV) | 15.9   | 10.2   | 8.9      | 9.8      | 38.5 | 15.6 |
| Ulnar   |        |        |          |          |      |      |
| MCV (m/s) | 56     | 61     | 51       | 48       | 58.7 | 5.1  |
| DL (ms)  | 2.4    | 2.7    | 2.6      | 2.3      | 2.59 | 0.39 |
| CMAP (mV) | 11.4   | 11.4   | 9.1      | 7.9      | 5.7  | 2.0  |
| SCV (m/s) | 46     | 48     | 49       | 50       | 54.8 | 5.3  |
| SNAP (μV) | 12.3   | 12.8   | 9.3      | 6.4      | 35.0 | 14.7 |
| Tibial  |        |        |          |          |      |      |
| MCV (m/s) | 51     | 44     | 39       | 43       | 48.5 | 3.6  |
| DL (ms)  | 4.0    | 3.7    | 3.4      | 3.5      | 3.96 | 1.00 |
| CMAP (mV) | 8.2    | 11.4   | 8.6      | 12.9     | 5.8  | 1.9  |
| Sural   |        |        |          |          |      |      |
| SCV (m/s) | 45     | NE     | NE       | NE       | 51.1 | 5.9  |
| SNAP (μV) | 3.1    | NE     | NE       | 17.2     | 6.7  | 6.7  |

CMAP: compound muscle action potential. DL: distal latency. F: female; L: left; M: male; MCV: motor conduction velocity, ND: not described, NE: not elicited, R: right, SCV: sensory conduction velocity, SD: standard deviation, SNAP: sensory nerve action potential. The control values are based on the textbook by Jun Kimura, Oxford University Press, Electrodiagnosis in diseases of nerve and muscle: principles and practice, Third edition.
lar cholangiocarcinoma (cT2bN1M0, stage IIIb), left he-
peatectomy, caudal lobectomy, extrahepatic bile duct re-
sction, and choledochojejunostomy were performed. The re-
sected specimen included a well-circumscribed mass lesion
(Fig. 2A). Unexpectedly, no malignancy was identified; in-
stead, storiform fibrosis (Fig. 2B) and lymphoplasmacytic
infiltration (Fig. 2C) with IgG4-positive cells (Fig. 2D) were
observed.

At two months after surgery, the patient developed limb
numbness (bilateral planter dysesthesia appeared, which as-

Figure 1. Radiological and pathological findings of the patient (case 1). A coronal T2-weighted im-
age (A) and T2 fat-suppression image (B). (A) The initial presentation 81 years of age. The arrow indi-
cates the levator palpebrae superioris muscle. The arrowhead indicates the lacrimal gland. En-
largement of the left levator palpebrae superioris and bilateral lacrimal glands is evident. (B) After
treatment with prednisolone (10 mg/day) for one month, the lacrimal glands returned to a normal size
and the enlargement of the levator palpebrae superioris in the left eye was reduced. Sural nerve bi-
opsy (C-D), (C) Hematoxylin and Eosin (H&E) staining. Epineurial perivascular lymphocytic infil-
tration was evident. IgG4-positive cells were not evident (not shown). (D) Epoxy resin-embedded trans-
verse sections stained with toluidine blue. Reduction of the myelinated fibers, and thin myelinated
clusters were observed, indicating the occurrence of axonal degeneration. Lip biopsy (E-H). (E) H&E
staining. Marked inflammatory cell infiltration was observed. Duct destruction was not evident. (F-
H) Immunohistochemistry. (F) Infiltration of CD138-positive plasma cells, which were stained in
brown, was evident. (G-H) IgG4-positive cells (H) accounted for >70% of the IgG-positive cells (G).
Scale bars indicate 50 μm.
cended to the knee within a week and was soon followed by dysesthesia of both hands). A neurological examination revealed bilateral weakness of the distal lower limbs (grade 4 according to the Medical Research Council Scale for Muscle Strength), sensory disturbance (decreased sensations of touch and vibrations in the distal lower limbs), and abnormal ankle jerk (absent on the left side and decreased on the right side).

A laboratory examination revealed hypergammaglobulinaemia with β-γ bridging without a monoclonal band. The serum IgG level was 1,865 mg/dL (reference: <1,700 mg/dL) and the IgG4 level was elevated at 712 mg/dL (reference: <117 mg/dL). Autoantibody screening was negative. A nerve conduction study found axonal neuropathy with a pattern of mononeuritis multiplex (Table 1). Sural nerve biopsy detected vascular occlusion, recanalization, and epineurial fibros...
physitis, inflammatory pseudotumors, and parenchymal brain disease are common in hypertrophic pachymeningitis, hypostics (5). The neurological manifestations of IgG4-related disease, with scarce case reports, little is known about its clinicopathological characteristics (5). The neurological manifestations of IgG4-related disease are common in hypertrophic pachymeningitis, hypophysitis, inflammatory pseudotumors, and parenchymal brain involvement, while neuropathy is rare (except in the orbital or paravertebral areas), with a frequency of <1% among patients with IgG4-related disease (10). Until now, most reports on IgG4-related neuropathy have addressed the focal involvement of the nerve adjacent to the IgG4-related perineurial lesion, particularly in the orbital area, and reports on peripheral neuropathy of the limbs are scarce (11).

Regarding the pathological diagnosis of neuropathy, without evident IgG4-positive plasmacytic infiltration, neither of the cases fulfilled the histological criteria for IgG4-related disease; instead, both cases met the diagnostic histopathological criteria for probable vasculitic neuropathy (Peripheral Nerve Society Guideline 2010), with findings of primary axonal neuropathic changes without significant demyelination, perivascular inflammation, or chronic vascular damage (12). Table 2 presents a summary of cases of IgG4-related disease complicated by peripheral neuropathy. Ohyama et al. analyzed 149 consecutive patients with inflammatory neuropathies and reported that IgG4 was involved, especially in patients with primary systemic vasculitis (13). We propose two different pathomechanisms underlying peripheral neuropathy related to IgG4-related disease. One is consistent with the characteristic pathological findings of IgG4-related disease, and the other is associated with vasculitis due to a systemic autoimmune condition without significant infiltration of IgG4-positive plasma cells.

In 2013, Ohyama et al. reported the first case of IgG4-related peripheral neuropathy with marked fibrosis and epineural IgG4-positive plasmocytic infiltration (6). The patient showed local skin lesions in the lower limbs without systemic involvement of IgG4-related disease. Since this report, no case of IgG4-related neuropathy with a similar pathophysiology has been described, suggesting that focal perineural infiltration adjacent to the skin lesion occurred in the first case by Ohyama et al. The same group reported a case of neuropathy with tumefactive cellular infiltration without IgG4-positive plasma cells or fibrosis in a patient with generalized IgG4-related lymphadenopathy (14). Additionally, Suzuki et al. described the case of a patient with anemia and limb dysesthesia with pain who underwent a bone marrow biopsy with a clinical diagnosis of multiple myeloma. The patient unexpectedly showed marked IgG4-positive lymphoplasmocytic infiltration in the bone marrow, leading to the diagnosis of IgG4-related disease, and excluding multiple myeloma (15).

From the viewpoint of therapy, in the case reported by Ohyama et al., the patient responded well to prednisolone (6). Importantly, in the case reported by Suzuki et al., the symptoms of neuropathy were refractory to prednisolone (15). Contrarily, other IgG4-related symptoms, including those of the bone marrow, were resolved with prednisolone treatment. In our cases, the response to prednisolone was refractory (Case 1) or partial (Case 2) (Table 2), although it is possible that Case 1 could have responded if we had administered a higher dose of prednisolone, such as 30 mg/day (the recommended glucocorticoid regimen for the
treatment of IgG4-related disease is prednisolone or predni-
sone at a dose of 0.4-0.6 mg/kg/day (16)). Contrary to the
case reported by Ohyama et al. (6) in which the condition
was limited to a local response, our cases, together with the
cases reported by Yokoi et al. and Suzuki et al. (14, 15), im-
ply that systemic autoimmune conditions are involved in the
pathogenesis of neuropathy related to IgG4-related disease
addition to the previously proposed IgG4-related peripheral
neuropathy as focal invasion, our cases suggest that a type
of vasculitis occurs secondary to the systemic IgG4-related
conditions.

To conclude, we presented two cases of IgG4-related dis-
ease with ptosis (case 1) and a pseudotumor of the bile duct
(case 2). These cases have educational value and contribute
ease with ptosis (case 1) and a pseudotumor of the bile duct
(Table 2).

### Table 2. Summary of the Patients with IgG4-related Disease, with Systemic or Local Involvement, Accom-
panied by Peripheral Neuropathy.

|                      | Case 1 | Case 2 | Yokoi et al. (14) | Suzuki et al. (15) | Ohyama et al. (6) |
|----------------------|--------|--------|-------------------|-------------------|-------------------|
| Age/sex              | 81/F   | 69/M   | 56/M              | 78/M              | 55/M              |
| Duration of neuropathy (months) | 1      | 1      | 72                | 5                 | 14                |
| Serum IgG4 (mg/dL)   | 1,310  | 712    | 328               | 1,290             | 259               |
| Serum IgG4/IgG (%)   | 47     | 38     | 10                | 24                | 10                |
| Other autoantibodies that tested positive | Ro/SSA | None   | Ro/SSA DNA TPO    | ND                | ANA               |
| Systemic involvements | PNS    | SC     | Ly                | BM                | None              |
|                      | SG SMG | Ly     | HSM               | HSM               | (Local skin lesion) |
| IgG4-pathology-confirmed tissues | Lip    | Bile duct | Lymph node | BM | Skin |
| Sural nerve biopsy   | -      | -      | -                 | -                 | +                 |
| IgG4-positive lymphoplasmacytic invasions | -      | -      | -                 | -                 | +                 |
| Suggestive of vasculitis | +      | +      | +                 | +                 | -                 |
| Type of IgG4-RD      | Systemic | Systemic | Systemic | Systemic | Local |
| IVMP                 | -      | -      | -                 | -                 | +                 |
| Prednisolone (mg/day) | 10     | 30     | 0.6 mg/kg/day     | 30                | 30                |
| Duration (weeks)     | 8      | 5      | ND                | 8                 | 3                 |
| Response to glucocorticoid therapy | (Refractory) | Partial (weakness improved) | Good | Refractory | Good |

ANA: antinuclear antibody, BM: bone marrow, DNA: anti-DNA antibody, EOM: extraocular muscle, HSM: hepatosplenomegaly, IgG4-RD: IgG4-related disease, IVMP: intravenous methylprednisolone, LG: lacrimal gland, Ly: lymphadenopathy, ND: not described, NT: not tested, PNS: paranasal sinus, RPF: retroperitoneal fibrosis, SC: sclerosing cholangitis, SG: salivary gland, SMG: submandibular gland, Ro/SSA: anti-Ro/SSA antibody, La/SSB: anti-La/SSB antibody, Tg: anti-thyroglobulin antibody, TPO: anti-thyroid peroxidase antibody

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Consent for publication

Written informed consent for publication was obtained from the patients.

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