【 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 in-
volvement 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 cho-
langitis (case 2), respectively. In both cases, sural nerve biopsy indicated vasculitis as the underlying patho-
physiology; the peripheral neuropathy was refractory to corticosteroid therapy. In contrast to the previously
proposed pathomechanism of IgG4-related neuropathy (direct lymphoplasmacytic infiltration), the pathologi-
cal 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

Introduction

   Immunoglobulin G4 (IgG4)-related disease is a relatively
new and emerging systemic autoimmune condition charac-
terized by a distinctive histopathological appearance of lym-
phoplasmacytic 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 cho-
langitis (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 dis-
ease, 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 neuro-
pathy 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 in-
filtration have been reported since then. Thus, the clinicopa-
thological characteristics of peripheral neuropathy in IgG4-
related disease are unclear. We herein report two cases of
IgG4-related disease with peripheral neuropathy.

Case Reports

Case 1

   An 81-year-old Japanese woman presented with a 6-
month history of unilateral ptosis that appeared after a few

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Table 1.　Nerve Conduction Study.

Age/sex		Case 1 81/F		Case 2 69/M		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	NE	17.2	6.7

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.

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

days of eyelid swelling, and a 1-month history of plantar dysesthesia. Surprisingly, she had a longstanding medical history of immunological complications, starting with a 20-year history of sinusitis and hypothyroidism due to thyroiditis. She developed sialadenitis at 66 years of age, allergic rhinitis at 67 years of age, and right submandibular gland enlargement at 68 years of age. However, from the 61 to 81 years of age, she did not receive any immunotherapy because her symptoms were thought to be non-specific or related to aging. A neurological examination at 81 years of age revealed left ptosis. With the exception of left ptosis (both pupils were equally reactive to light), and right predominant plantar dysesthesia, which she described as a sensation of bubbling water on her skin, she showed no further signs of neurological disturbance.

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 cytoplasmic 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 superioris, 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 epineural 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 superioris 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 superioris 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.

Case 2

A 69-year-old Japanese man was referred to us with limb numbness that had appeared one month before admission. At 68 years of age, he had undergone surgery for oral cancer (squamous cell carcinoma), which did not require chemotherapy or radiotherapy. At one year after surgery, follow-up CT showed right hilar and left axillary lymphadenopathy and a low-density area in the liver with a dilated left bile duct. Positron emission tomography/CT showed lesions in the liver and bilateral supraclavicular, right hilar, left axillary, and hepatoduodenal mesenteric lymph nodes. Biopsy of the right hilar and left axillary lymph nodes detected no evidence of malignancy. After the preoperative diagnosis of hi-
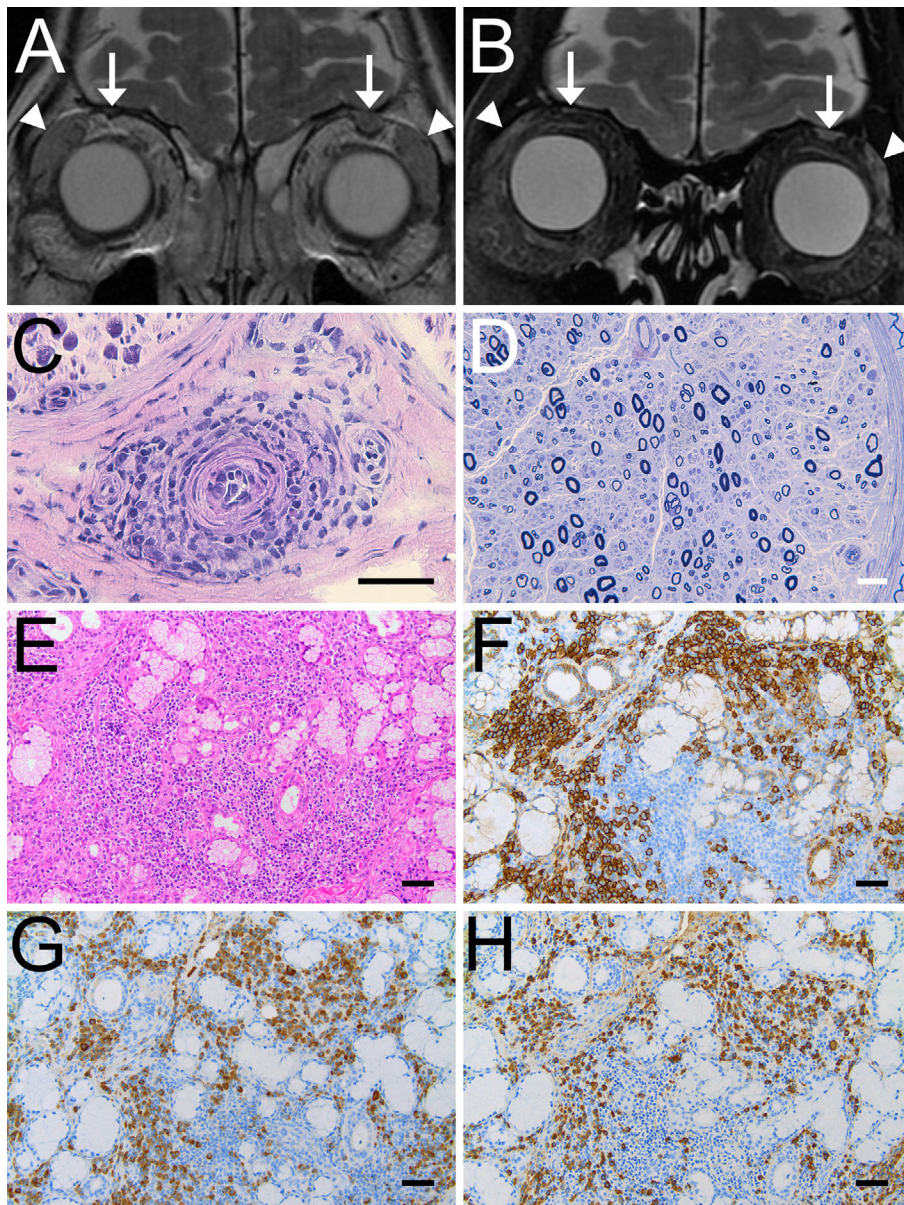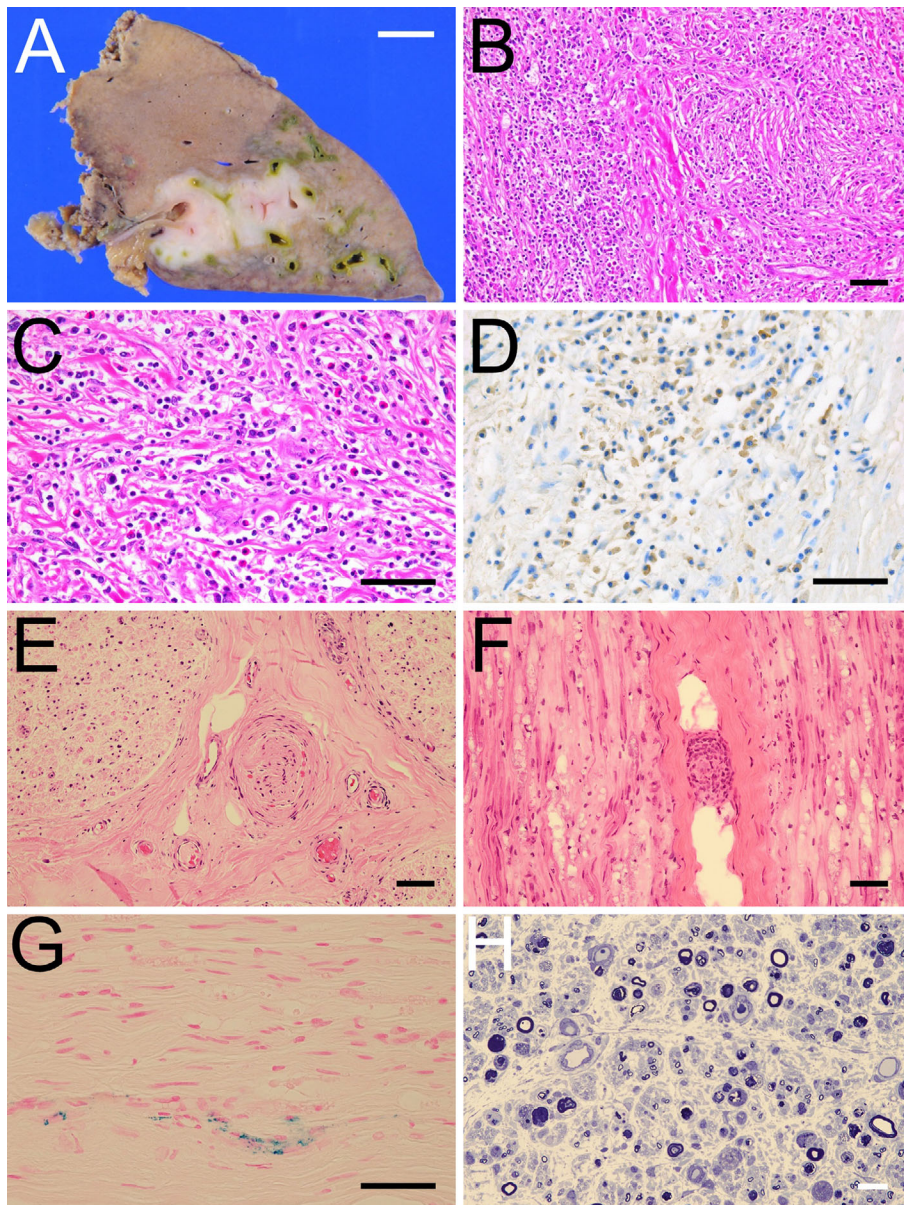
Figure 1. Radiological and pathological findings of the patient (case 1). A coronal T2-weighted image (A) and T2 fat-suppression image (B). (A) The initial presentation 81 years of age. The arrow indicates the levator palpebrae superioris muscle. The arrowhead indicates the lacrimal gland. Enlargement 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 biopsy (C, D). (C) Hematoxylin and Eosin (H&E) staining. Epineural perivascular lymphocytic infiltration was evident. IgG4-positive cells were not evident (not shown). (D) Epoxy resin-embedded transverse 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.

lar cholangiocarcinoma (cT2bN1M0, stage IIIb), left hepatectomy, caudal lobectomy, extrahepatic bile duct resection, and choledochojejunostomy were performed. The resected specimen included a well-circumscribed mass lesion (Fig. 2A). Unexpectedly, no malignancy was identified; instead, 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 2. Surgical and pathological findings of the patient (case 2). (A-D) Sclerosing cholangitis. (A) The resected left liver and caudate lobe (19 cm×10 cm×5 cm), including a pseudotumor-like lesion (3.2 cm×3.0 cm×1.6 cm) at the hepatic hilum. (B) Hematoxylin and Eosin (H&E) staining showed storiform fibrosis and obliterative phlebitis. (C) H&E staining. (D) Immunohistochemistry. Lymphoplasmacytic infiltration (C) with IgG4-positive cells (D) was evident, accounting for >45% of the IgG-positive cells, with more than 50-60 IgG4-positive plasma cells per high-power field. (E-H) Sural nerve biopsy. (E-G) H&E staining. Vascular occlusion, vascular recanalization, and epineural fibrosis were observed (E). Epineural lymphocytic infiltration was observed (F) without evident IgG4-positive cells (not shown). Hemosiderin deposits are shown (G). (H) Epoxy resin-embedded transverse sections stained with toluidine blue. Myelin ovoids were evident. Scale bars indicate 1 cm in A and 50 μm in B-H.

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 hypergammaglobulinemia 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 epineural fi-

brosis (Fig. 2E). Moreover, lymphocytic infiltration without IgG4-positive cells (Fig. 2F), hemosiderin deposition (Fig. 2G), and axonal neuropathy (Fig. 2H) were observed. Based on these results, a diagnosis of mononeuritis multiplex complicated with IgG4-related sclerosing cholangitis was made. The patient was treated with oral prednisolone (0.5 mg/kg/day), and after one month his muscle weakness fully recovered; however, the sensory disturbances remained unchanged.

Discussion

In case 1, the patient's longstanding immunological history of sinusitis, thyroiditis (Riedel's), sialadenitis (Mikulicz's disease, Küttner's tumor), rhinitis, orbital disease, peripheral neuropathy, retroperitoneal fibrosis (Ormond's disease), pancreatitis, and lymphadenopathy were explained by a single etiology of IgG4-related disease as the underlying cause. Regarding sclerosing cholangitis and pancreatitis, due to the non-specific signs and pseudotumor-like lesions, patients with IgG4-related disease are often misdiagnosed with a malignancy. In some cases, however, IgG4-related pathophysiology is identified on the biopsy before the surgical procedure (7). As in case 2, when the patient is asymptomatic and in the absence of specific biopsy findings, surgery is inevitably required to establish a diagnosis. In retrospect, the laboratory findings in case 2, of hypergammaglobulinemia with β-γ bridging, which were highlighted as a key feature in the report by Hamano et al. (4), was a clue to diagnosis prior to the surgical intervention.

In clinical practice, our cases highlight two noteworthy points. First, regarding the ptosis in case 1, although ophthalmic involvement is frequent in IgG4-related disease, leading to IgG4-related ophthalmic disease (8), IgG4-related disease is often neglected in the differential diagnosis of ptosis. To our knowledge, there is no report on ptosis caused by the enlargement of the levator palpebrae superioris due to IgG4-related disease. In case 1, unilateral enlargement of the levator palpebrae superioris muscle was revealed by MRI, and myositis or edema was noticed. Among the differential diagnoses of orbital myositis associated with systemic inflammatory and autoimmune disease (except for thyroid-associated orbitopathy), IgG4-related disease is the most frequently noted, with a prevalence of 15-37% among patients with IgG4-related disease; however, extraocular muscle involvement mainly focuses on muscles other than the levator palpebrae superioris (9). In case 1, ptosis was the initial clue to the diagnosis; hence, enlargement of the levator palpebrae superioris due to IgG4-related disease should be considered in the differential diagnosis of patients with ptosis.

Second, although peripheral neuropathy is known to be complicated with 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 perineural 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 lymphoplasmacytic 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

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

	Case 1	Case 2	Reference (14)	Reference (15)	Reference (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 La/SSB Tg TPO	None	Ro/SSA DNA TPO	ND	ANA
Systemic involvements	PNS Thyroid SG SMG LG EOM RPF Pancreas Ly	SC Ly	Ly HSM	BM HSM Ly	None (Local skin lesion)
IgG4-pathology-confirmed tissues	Lip SMG	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 grand, 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

treatment of IgG4-related disease is prednisolone or prednisone 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), imply that systemic autoimmune conditions are involved in the pathogenesis of neuropathy related to IgG4-related disease (Table 2).

To conclude, we presented two cases of IgG4-related disease with ptosis (case 1) and a pseudotumor of the bile duct (case 2). These cases have educational value and contribute to medical knowledge by highlighting the need to include IgG4-related disease in the differential diagnosis of ptosis and cholangiocarcinoma, and by emphasizing the importance of the laboratory finding of hypergammaglobulinemia with β-γ bridging as a clue to the diagnosis. Furthermore, in 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.

Written informed consent for publication was obtained from the patients.

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

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