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Case study

Mononeuritis multiplex with tumefactive cellular infiltration in a patient with reactive lymphoid hyperplasia with increased immunoglobulin G4–positive cells☆

Satoshi Yokoi MD[a], Yuichi Kawagashira MD, PhD[a], Ken Ohyama MD[a], Masahiro Iijima MD, PhD[a], Haruki Koike MD, PhD[a], Hirohisa Watanabe MD, PhD[a], Akiko Tatematsu MD, PhD[b], Shigeo Nakamura MD, PhD[b], Gen Sobue MD, PhD[a,*]

[a]*Department of Neurology, Nagoya University Graduate School of Medicine, Nagoya466-8550, Japan*
[b]*Department of Pathology, Nagoya University Graduate School of Medicine, Nagoya466-8550, Japan*

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Summary We describe a 54-year-old man with mononeuritis multiplex and reactive lymphoid hyperplasia with increased immunoglobulin G4 (IgG4)–positive cells. Asymmetrical numbness and weakness had advanced stepwise for 6 years. Serum immunoglobulin G, IgG4, and immunoglobulin E levels were elevated, whereas M protein was not detected. Chest and abdominal computed tomography showed generalized lymphadenopathy. Inguinal lymph node biopsy revealed expansion of the interfollicular area with infiltration of IgG4-positive cells, of which the absolute number was greater than 100 per high-power field, and the percentage of IgG4+/immunoglobulin G+ plasma cells was 33%. Sural nerve biopsy disclosed axonal neuropathy with tumefactive lymphoid infiltrate in epineurium, but IgG4-positve plasma cells and fibrosis were not detected. Symptoms and laboratory data were improved with oral glucocorticoid therapy at a dose of 0.6 mg/kg per day. Although the causal mechanisms of neuropathy should be determined in future studies, peripheral nerve involvement may occur in patients with reactive lymphoid hyperplasia with increased IgG4-positive cells.

1. Introduction

Immunoglobulin G4 (IgG4)–related disease (IgG4-RD), which was first described in 2001 in patients with autoimmune pancreatitis associated with lymphoplasmacytic infiltration and fibrosis [1], is recognized as a new disease group that affects multiple organs. In addition to pancreas, numerous case series have expanded the spectrum of this disorder and shown the involvement of multiple organs, including lacrimal glands, kidneys, retroperitoneum, thyroid, and liver, presenting IgG4-positive plasma cells with fibrotic or sclerotic changes [2].

Lymph nodes are also affected with IgG4-RD, and criteria for IgG4-related lymphadenopathy have been developed [3]. Both the number of IgG4-positive plasma cells and the ratio of IgG4+/immunoglobulin G+ (IgG+) plasma cells are considered to be important, but the discussion continues [4,5]. Cases that do not meet the criteria are named reactive lymphoid hyperplasia with increased IgG4-positive cells,

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* Corresponding author.
E-mail address: sobueg@med.nagoya-u.ac.jp (G. Sobue).

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and careful follow-up is recommended to diagnose whether IgG4-RD is present.

In the classical form of IgG4-RD, peripheral neuropathy may occur as a result of infiltration of IgG4-positive plasma cells and fibrosis in the epineurium [6]. On the other hand, concomitance of neuropathy in patients with IgG4-related lymphadenopathy has not yet been reported. Here, we described a case of reactive lymphoid hyperplasia with increased IgG4-positive cells and mononeuritis multiplex with tumefactive lymphoid infiltration in the epineurium of a sural nerve biopsy specimen. The continuum between IgG4-RD and reactive lymphoid hyperplasia with increased IgG4-positive cells is discussed from the viewpoint of the peripheral nerve involvement.

2. Case report

A 56-year-old man was admitted to our hospital with complaint of mild numbness and weakness in all extremities. He had neither a special history of surgical operation nor heavy use of alcohol, although mild lumbar disc herniation had been pointed out. Numbness in his right leg began suddenly 6 years before our clinical evaluation. One month later, numbness progressed in other limbs in the same way, and weakness in his right hand appeared. He could not extend his fourth and fifth fingers of the right hand, and muscle atrophy was observed in the right interossei muscles. Muscle weakness and numbness of all extremities became conspicuous gradually.

On admission, physical examination revealed brownish pigmentation of skin in the lower limbs and pitting edema (Fig. A). Sicca syndrome was absent. Neurologic examination revealed mild sensory disturbance in all extremities distally from wrist and ankle. Touch, pain, vibratory, and joint sensations of all extremities, which were predominant on the right side, were mildly reduced. Mild weakness in both hands and legs was also present, and muscle atrophy of interossei muscles was observed in the right hand, whereas no muscle atrophy of other extremities was observed. Romberg sign was positive. There were no abnormalities in the cranial nerves or the autonomic nervous system. Deep tendon reflexes were all absent. Plantar responses were flexor on both sides.

Laboratory examination showed that hemoglobin level was 12.4 mg/dL and a normal white blood cell count of 7500/mm^3 with 6% eosinophils. Erythrocyte sedimentation rate and C-reactive protein (CRP) were elevated to greater than 100 mm/h (normal <15) and 3.2 mg/dL (normal <0.3), respectively. Other abnormal values included serum IgG 3322 mg/dL (normal <1700), IgE 10143 IU/mL (normal <202), IgA 735 mg/dL (normal <410), IgG4 328 mg/dL (normal <105), interleukin (IL) 6 of 13 pg/mL (normal <4), anti–SSA antibody of 91.6 index (normal <10.0), anti-DNA antibody of 7.4 IU/mL (normal <6), anti–thyroid peroxidase antibody of 17.8 IU/mL (normal <16).

Ophthalmologic and otological examinations did not fulfill the criteria of Sjögren syndrome. Myeloperoxidase antineutrophil cytoplasmic antibody and cytoplasmic antineutrophil cytoplasmic antibody were negative. M protein was not detected by immunoelectrophoresis. Serum vascular endothelial growth factor was 536 pg/mL. No endocrine abnormalities, including adrenocorticotropic hormone, cortisol, and thyroid hormone, were found. Urinary examination revealed that both protein and N-acetyl-β-D-glucosaminidase were elevated to 0.61 g/d and 15.2 U/d, respectively. Cerebrospinal fluid protein was elevated to 86 mg/dL with normal cell count.

In a nerve conduction study performed with a standard method [7], motor nerve conduction velocities were normal in bilateral median, ulnar, and tibial nerves, but compound muscle action potentials in the right median nerve and right tibial nerve were decreased to 1.7 and 3.2 mV, respectively. Prolonged distal latencies were observed to 4.0 milliseconds in the right ulnar nerve, 6.0 milliseconds in the right tibial nerve, and 5.8 milliseconds in the left tibial nerve. Sensory nerve action potentials in the right ulnar nerve and bilateral sural nerves were not elicited. Electrophysiological feature showed mononeuritis multiplex in accordance with clinical presentation.

Chest and abdominal computed tomographic (CT) scans showed generalized multiple lymphadenopathy whose sizes were approximately 1 cm (Fig. B). Mild hepatosplenomegaly was also present. Body cavity effusion was absent. Inguinal lymph node biopsy revealed expansion of the interfollicular area with infiltration of lymphocytes, plasma cells, and eosinophils (Fig. C and D). The lymph node structure was preserved, and germinal centers were regressive. Hyalinized blood vessels were also seen but seldom penetrated germinal centers. Numerous IgG4-positive plasma cells were present (Fig. E-G), numbering 114 per high-power field, and the ratio of IgG4+/IgG+ plasma cells was 33%, measured at 3 sites. Immunostaining revealed no immunoglobulin light chain restriction. Fibrosis and malignant findings were absent.

A sural nerve biopsy specimen, which was processed as previously described [8], revealed moderate decrease in myelinated fiber density on cross section (Fig. H). In teased-fiber preparations, axonal degeneration was found (8.5%), whereas segmental demyelination was not present. Uncompacted myelin lamellae, which was usually observed in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, and skin changes) syndrome, was not detected by electron microscopy.

In longitudinal section fixed in 10% formalin solution and stained with hematoxylin and eosin, epineural tumefactive infiltration of lymphocytes and eosinophils were observed (Fig. I and J). Immunostaining revealed the presence of CD20+ lymphocytes and CD8+ lymphocytes, whereas the population of CD4+ lymphocytes was scarce. Infiltration of lymphocytes and eosinophils in the epineurium of sural nerve specimens corresponded to those in the lymph node specimens. A few CD138+ lymphocytes were observed in the epineurium. However, IgG4-positve plasma cells (Fig. K) and fibrosis in the epineurium were not observed. Amyloid deposition in the endoneurium was not detected using Congo red staining.