**Observation**

**IgG4-Related Neuropathy**

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**Importance:** The newly recognized entity IgG4-related disease (IgG4-RD) is characterized by an elevated IgG4 serum concentration and tissue infiltration by IgG4-positive plasma cells. We describe, for the first time, the clinical features and nerve biopsy findings of a patient with IgG4-RD who presented with neuropathy in the extremities.

**Observations:** A 55-year-old man had histopathologically defined IgG4-RD that manifested as sensory-motor neuropathy. The neuropathic features were multiple mononeuropathies with electrophysiological findings suggestive of axonal neuropathy. Marked thickening with abundant collagen fibers and infiltration of IgG4-positive plasma cells were observed in the epineurium of the biopsied sural nerve. A moderate degree of myelinated fiber loss without evidence of segmental demyelination was present, whereas necrotizing vasculitis was not found. Oral prednisolone therapy ameliorated the neuropathic symptoms.

**Conclusions and Relevance:** This case of IgG4-RD presented as sensory-motor neuropathy with pain and sclerosis of the skin in the extremities. The differential diagnosis of neuropathy should include IgG4-RD.


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**REPORT OF A CASE**

A 55-year-old man had pigmentation and sclerosis of the skin around the left ankle that first presented 20 years ago. When ulcers of the skin occasionally occurred, he was treated with betamethasone. However, the skin change did not disappear and remained around the left ankle. One and a half years ago, the patient was diagnosed as having diabetes and has been receiving oral medication to maintain normal serum glycated hemoglobin values (6.0% [reference range, 4.6%-5.7%; to convert to proportion of total hemoglobin, multiply by 0.01]). Ophthalmologists and nephrologists did not note any diabetic complications. At that time, the skin change spread to the lower left leg under the knee and subsequently to the lower right leg. The patient felt numbness and continuous pain in the lower legs 4 months later. Thereafter, the patient noticed a loss of grasping power in the hands. He was admitted to our hospital as the symptoms gradually worsened.

On admission, body mass index (calculated as weight in kilograms divided by height in meters squared) was 20.2. In both
lower legs, pigmentation and sclerosis of the skin with ulcerations and with and without scars were found (Figure, A). The patient was alert and well oriented, and his cranial nerves were intact. He had mild muscular weakness in his distal limbs, and his ability to grasp had decreased (right, 23 kg; left, 16 kg). There was no sign of

Figure. Clinical photograph and biopsy findings. A, Skin pigmentation with ulcers. B and C, Skin biopsy findings. Fibrosis and infiltration of inflammatory cells were observed in the subcutaneous tissue in addition to numerous IgG4-positive plasma cells (hematoxylin-eosin [B] and IgG4 immunostain [C], scale bar = 50 µm). D-H, Sural nerve biopsy findings. D and E, Marked thickening with abundant collagen fibers and infiltration of IgG4-positive plasma cells were observed in the epineurium (hematoxylin-eosin [D] and azan [E], scale bar = 500 µm). F, Perineural infiltration of inflammatory cells was observed (hematoxylin-eosin, scale bar = 30 µm). G, More than 10 IgG4-positive plasma cells exist in the epineurium (IgG4 immunostain, scale bar = 30 µm). H, There was a moderate reduction in large and small myelinated fibers (toluidine blue, scale bar = 50 µm).
The serum vascular endothelial growth factor level was elevated (259 mg/dL [reference range, 5-105 mg/dL; to convert to grams per liter, multiply by 0.01]). Additionally, the serum IgG4 level was elevated (259 mg/dL [reference range, 870-1700 mg/dL; to convert to grams per liter, multiply by 0.001]; and IgG, 2544 mg/dL [reference range, 0-1500 mg/dL; to convert to grams per liter, multiply by 10]; IgE, 847.2 kU/L [reference range, 0-145 kU/L; to convert to milligrams per liter, multiply by 7.03]).

Muscle biopsy showed muscle atrophy. On both sides, the deep tendon reflexes were mildly diminished in the upper and lower extremities. Flexor plantar responses were observed on both sides. Severe spontaneous pain existed in the lower legs. The sensation of pain was moderately diminished in both lower legs, and the sensation of temperature was mildly diminished in the right lower leg. The sensation of vibration was severely diminished in both feet. The sensations of light touch and position had not decreased. The patient could not walk a long distance because of leg pain. Although he had dysesthesia in both hands, objective sensory disturbance in the upper limbs was not detected, except for a mild reduction in vibration sensation.

The IgA, IgE, and IgG levels increased (IgA, 569 mg/dL; IgE, 847.2 kU/L; and IgG, 2544 mg/dL; to convert to grams per liter, multiply by 0.01). The IgA level became normal after 3 weeks (IgA, 375 mg/dL; IgG, 1443 mg/dL) and his IgG4 level decreased in the median and ulnar nerves, whereas the sensory nerve action potentials were normal. A sensory-motor neuropathy was not evoked in the sural nerve.

A skin biopsy of the left lower leg showed marked fibrosis and infiltration of IgG4-positive cells in the subcutaneous tissue (Figure, B and C). There was no evidence of necrotizing vasculitis. The frequency of IgG4-positive cells as a percentage of IgG-positive cells in the skin was approximately 30%.

A sural nerve biopsy revealed marked thickening with abundant collagen fibers and infiltration of IgG4-positive plasma cells in the epineurium (Figure, D and E). Although infiltration of inflammatory cells was abundant in the epineurial perivascular areas, findings suggestive of necrotizing vasculitis such as occlusion of blood vessels or fibrinoid necrosis were not found. Immunohistochemical assessments revealed a mixture of CD20-positive B lymphocytes, CD3-positive T lymphocytes, CD68-positive macrophages, and IgG-positive plasma cells in the perineurium and the epineurial perivascular areas. The CD20-positive B lymphocytes were especially abundant in the epineurial perivascular areas, while they were scarce in the perineurium. There were no inflammatory cells in the endoneurium. Clusters of IgG4-positive plasma cells were observed in the perineurial tissue. The number of IgG4-positive plasma cells was higher than 10 per high-power field (Figure, F and G). Moderate decreases in the densities of large and small fibers were observed (Figure, H). A few clusters of myelinated fibers, ie, potentially regenerating fibers, were observed. A teased-fiber study indicated axonal degeneration (11.9%) without evidence of segmental demyelination. Amyloid deposition was not detected with Congo red staining.

Because the patient was diagnosed as having IgG4-RD, he was treated with oral prednisolone therapy (30 mg/d). After starting prednisolone, his symptoms of numbness and continuous pain gradually improved and his grasping power increased in 3 weeks (right, 36 kg; left, 30 kg). He could walk a long distance. Blood tests showed that his IgA and IgG levels became normal after 2 weeks (IgA, 375 mg/dL; IgG, 1443 mg/dL) and his IgG4 level became normal after 3 weeks (IgG4, 102 mg/dL).

**Table. Nerve Conduction Study Results**

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Patient</th>
<th>Controls, Mean (SD)</th>
</tr>
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<tbody>
<tr>
<td>Median</td>
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<td></td>
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<tr>
<td>Motor</td>
<td>MCV, m/s</td>
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<td>DL, ms</td>
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<tr>
<td></td>
<td>CMAP, mV</td>
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<td>Ulnar</td>
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<td>Tibial</td>
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<td>NE</td>
</tr>
<tr>
<td></td>
<td>SNAP, µV</td>
<td>NE</td>
</tr>
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</table>

Abbreviations: CMAP, compound muscle action potential; DL, distal latency; MCV, motor conduction velocity; NE, not elicited; SCV, sensory conduction velocity; SNAP, sensory nerve action potential.

*Control values are based on a previously published report.*

The entity of IgG-RD has been reported to involve a variety of organs, and some organ-specific diagnostic criteria for IgG4-RD have been proposed. However, there was normal, as were results of a cerebrospinal fluid examination. Findings on gallium 67 scintigraphy and on chest and abdomen computed tomographic, positron emission tomographic, and magnetic resonance imaging scans of the cranial, pituitary, and lumbar spinal cord did not show any apparent abnormalities.

Nerve conduction studies showed the existence of sensory-motor neuropathy (Table). Motor conduction velocities in the median, ulnar, and tibial nerves were normal (± 2 SDs of controls). The amplitudes of the compound muscle action potentials were preserved in the median and ulnar nerves but decreased in the tibial nerve. Additionally, the sensory conduction velocities were decreased in the median and ulnar nerves, whereas the sensory nerve action potentials were normal. A sensory nerve action potential was not evoked in the sural nerve.

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**COMMENT**

The entity of IgG-RD has been reported to involve a variety of organs, and some organ-specific diagnostic criteria for IgG4-RD have been proposed. However, there

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is no consensus on the diagnosis for IgG4-related peripheral neuropathy. According to the “Comprehensive Diagnostic Criteria for IgG4-RD, 2011,”6 the following items are necessary for diagnosis: (1) swelling or masses in single or multiple organs; (2) elevated serum IgG4 concentrations (>135 mg/dL); and (3) marked lymphocyte and plasma cell infiltration with IgG4-positive plasma cells (ratio of IgG4-positive/IgG-positive cells >40% and >10 IgG4-positive plasma cells per high-power field) and fibrosis in a histopathological examination. In our case, swelling of the peripheral nerves, elevated serum IgG4 concentration, and fibrosis with IgG4-positive plasma cell infiltration were identified. Thus, most of the characteristic features of IgG4-RD were present.

Focal ischemia resulting from the occlusion of vessels by infiltrating inflammatory cells or constriction by marked fibrosis could be considered mechanisms of IgG4-related neuropathy. The patient’s clinical symptoms showed multiple mononeuropathy patterns, and the findings from the sural nerve biopsy showed axonal neuropathy. These features, in addition to perivascular inflammatory cell infiltration, suggest that vasculitis was the cause of the neuropathy.7 However, there were no findings suggestive of necrotizing vasculitis. Recently, a few reports described intraorbital, trigeminal, and paravertebral nerve involvement.8,9 A pathological assessment revealed that the nerves were surrounded by inflammatory infiltration, including the infiltration of IgG4-positive plasma cells with fibrosis. Therefore, constriction by surrounding tissues was likely in such cases. Future studies are necessary to clarify the pathogenesis of neuropathy in IgG4-RD.

In conclusion, we describe the first case, to our knowledge, of IgG4-related neuropathy, which presented as sensory-motor neuropathy with pain and sclerosis of the skin in the extremities. The histopathological findings of a sural nerve biopsy indicated IgG4-RD, and oral prednisolone therapy was highly effective. The differential diagnosis for the mononeuritis multiplex type of neuropathy should include IgG4-RD.

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REFERENCES