Amyloid-like immunoglobulin M (IgM) deposition neuropathy associated with Waldenström macroglobulinemia is a rare phenotype of IgM-related neuropathy. The prominent clinical features are painful sensory-dominant neuropathy followed by distal motor weakness and atrophy over a long clinical course. Herein, we report a case of amyloid-like IgM deposition neuropathy that was successfully treated with rituximab (RTX).

Classification of evidence. This provides Class IV evidence that in patients with amyloid-like IgM deposition neuropathy associated with Waldenström macroglobulinemia, RTX therapy ameliorates motor neuropathy along with cutaneous macroglobulinosis and repeated RTX prevents their exacerbations. This was a single observational study without controls.

Case report. A 63-year-old man presented with weakness of his left fingers, which had started 3 days earlier. He had experienced tingling and numbness in distal portions of all extremities over the past 3 years and intermittent sharp pain in the lower limbs several times a day over the past 2 years. Physical examinations revealed left finger weakness without atrophy in the ulnar nerve region and symmetrical mild numbness with a glove and stocking distribution. He also had small reddish skin rashes on the distal legs, which changed into discrete blister-like papules within 2 to 3 weeks (figure, A). Laboratory examinations showed the presence of IgM-monoclonal gammopathy (IgM 1,231 mg/dL) and an increased number of lymphoplasmacytic cells in bone marrow, which confirmed the diagnosis of Waldenström macroglobulinemia. A nerve conduction study revealed a reduced compound muscle action potential (CMAP) (7.4 mV) in the left ulnar nerve (LUN) with normal distal latency and slightly decreased conduction velocity. Sensory nerve responses in the left median, ulnar, and bilateral sural nerves were absent.

Microscopic analysis of a sural nerve biopsy revealed amorphous amyloid-like aggregates in the endoneurium and subperineurium that were stained by an anti-IgM antibody (figure, B and C). A semithin section showed severe fiber loss (figure, D), and the aggregates were found to be composed of a filamentous material in electron microscopy (figure, E). Biopsy of the duodenal mucosa and skin rashes showed the same aggregates (figure, F and G). Amyloid-like IgM deposition neuropathy with cutaneous macroglobulinosis was diagnosed.

Initial treatment with IV immunoglobulin was ineffective. CMAP in LUN further worsened to 2.3 mV. RTX infusion therapy (375 mg/m², 4 weekly infusions) was introduced, and led to gradual improvement of weakness of the left fingers over 5 months, along with a significant decline of intermittent sharp pain in the lower limbs. The blister-like papules in the lower limbs alsoameliorated and changed to pigmented macules. The serum IgM level was markedly decreased (522 mg/dL) 5 months after the start of RTX.

Nine months after the start of RTX, CMAP in LUN had increased (11.0 mV), but the left extensor pollicis longus muscle showed gradual worsening of weakness with relapse of skin rashes and an increase in serum IgM (1,045 mg/dL). The second RTX therapy improved the weakness and skin rashes, but mild sensory disturbances in the distal limbs were unchanged.

The patient has undergone RTX therapy every 6 months for the following 2 years with no relapse of finger weakness and skin rashes. The serum IgM normalized 1 year after the reintroduction of RTX therapy and has subsequently remained within the normal range.

Discussion. Clinical courses and treatment have been reported for 7 cases of amyloid-like IgM deposition neuropathy. Sensory disturbances preceded development of weakness by 6 months to 20 years in 5 cases. Immune-mediated treatments, such as prednisolone, chlorambucil, and cyclophosphamide, plasma exchange, and RTX infusion were introduced in an early stage of development of weakness but resulted in poor improvement of limb weakness in 6 cases. One patient with mononeuropathy multiplex after 17 years of sensory neuropathy showed almost complete recovery of power after oral administration of cyclophosphamide.
The pathophysiology of amyloid-like IgM deposition neuropathy is unclear and may be heterogeneous. In addition to a direct effect of deposited materials on nerve fibers, a vasculitic process is suggested by clinicopathologic features such as acute-onset multiple mononeuropathy and epi-neurial inflammatory changes. In our patient, sural nerve biopsy findings indicated that sensory polyneuropathy is likely to result from progressive deposition of amyloid-like IgM and subsequent compression of nerve fibers. The acute-onset left ulnar neuropathy might emerge through an acute inflammatory process secondary to IgM deposition, given the time course. The favorable response of left ulnar neuropathy to RTX therapy may be induced by amelioration of secondary nerve inflammation as well as reduction of IgM production and deposition. Our patient is unique in that RTX therapy was effective for acute-onset motor weakness along with cutaneous macroglobulinosis and that repeated RTX infusions were beneficial for preventing exacerbations.

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