Case Report

Autopsy-proven case of paraneoplastic lower motor neuron disease with sensorimotor neuropathy due to Waldenström’s macroglobulinemia

Yasuhiro Suzuki,1,2 Hitoshi Aizawa,3 Kento Sakashita,1 Hideaki Kishi,1 Kenta Nomura,1 Kosuke Yoshida,1 Yoko Aburakawa,1 Kenji Kuroda,1 Chisato Murakami,2 Yasutaka Kakinoki4 and Takashi Kimura1

Departments of 1Neurology, 2Clinical Research, Asahikawa Medical Center, 4Department of Hematology, Asahikawa City Hospital, Asahikawa and 3Department of Neurology, Tokyo Medical University, Tokyo, Japan

We report a case of a male patient with a 19-year history of monoclonal and later polyclonal gammopathy who subsequently developed tetraparesis, bulbar palsy, and respiratory failure. Autopsy findings showed degeneration of the hypoglossal nuclei, prominent neuronal loss and atrophy in the anterior horn of the whole spinal cord despite the presence of mild astrocytosis, degeneration of the gracilis on one side, and infiltration of inflammatory cells, which included B cells and plasma cells in the anterior and posterior roots of the lumbar spinal cord, iliopectineus muscle, and perivascular area of the cervical cord. On immunostaining, cytoplasmic inclusions of phosphorylated transactivation response DNA-binding protein of 43 kDa were observed in the motor neurons and astrocytes of the hypoglossal nuclei and whole spinal cord. The final diagnosis was paraneoplastic lower motor neuron disease with sensorimotor neuropathy due to Waldenström’s macroglobulinemia.

Key words: anti-CD20 antibody, autopsy, paraneoplastic lower motor neuron disease, TDP-43, Waldenström’s macroglobulinemia.

INTRODUCTION

Waldenström’s macroglobulinemia (WM) was originally described in two patients in 1944. WM is defined as a lymphoplasmacytic lymphoma that develops in the bone marrow and is characterized by immunoglobulin M paraproteinemia.1 Primary symptoms of WM are anemia, hepatosplenomegaly, lymphadenopathy, hyperviscosity, and polyneuropathy. Neuropathies associated with WM are heterogeneous. Peripheral neuropathies affect 5–10% of WM patients, usually causing painless distal sensory loss and tremor due to damage to large-diameter myelinated nerve fibers, followed by muscle weakness and atrophy in the extremities.2 Several investigators have additionally shown that monoclonal paraproteinemia may be associated with the onset of motor neuron disease (MND) as opposed to the disease randomly occurring within the general population.3-5 To the best of our knowledge, only a few reports have evaluated the association with MND and definitively diagnosed monoclonal paraproteinemia due to WM during an autopsy.6,7 Moreover, little is known as to why there is degeneration of motor neurons in the anterior horn in paraproteinemia due to WM.

This report provides details on a case that was pathologically diagnosed as having lower MND with one side posterior funiculus after developing in conjunction with sensorimotor neuropathy associated with WM.

CLINICAL SUMMARY

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A 58-year-old, right-handed man was admitted to the hospital because of progressive dysesthesia in his distal upper and lower extremities. The patient had been in good health until 2 years prior to his admission for dysesthesia that extended into his distal lower extremities. One year prior to his admission, sensory disturbance developed in his upper distal extremities. There was no family history of the disease, even when considering his parents were cousins. Neurological examination showed glove and stocking type sensory disturbances primarily in his extremities on the right side, and hyporeflexia in his lower extremities. No plantar responses
were revealed, and there was no muscle weakness, bladder bowel disturbance, ataxia, or gait disturbance were detected. Laboratory examinations revealed that there was an increase in the erythrocyte sedimentation rate (28 mm/h, normal range: 2–10 mm/h) and IgM (584 mg/dL, normal range: 32–190 mg/dL). Serum protein electrophoresis revealed the existence of M-protein (IgM κ type). Anti-myelin-associated glycoprotein (MAG) antibody, antiganglioside antibodies, which included GM1 antibody, cryoglobulin, anti-Sjögren’s syndrome antigen A (SS-A) antibody, anti-SS-B antibody, proteinase 3 (PR3)-antineutrophil cytoplasmic antibody (ANCA), and myeloperoxidase (MPO)-ANCA were all negative. No Bence Jones protein was detected in a concentrated specimen of urine. A lumbar puncture was performed and indicated there was an increased concentration of protein (58 mg/dL, normal range: 10–40 mg/dL). There were no atypical lymphocytes or tumor-like cells noted in the cerebrospinal fluid. The motor-nerve conduction studies showed diffuse low amplitudes for the compound muscle action potentials, and slow velocity with the conduction blocks. Sensory nerve action potentials were not detected in either the hands or legs. A nerve biopsy of the right sural nerve identified a decrease in the large myelinated fibers, a few fibers with onion bulb formation, and thin myelinated fibers. These results demonstrated the presence of demyelinated degeneration. Taken together, these findings led to a diagnosis of sensorimotor neuropathy due to paraproteinemia. As the serum IgM gradually increased, a marrow biopsy was performed in the patient at 65 years of age. The biopsy revealed the specimen to be normocellular, with several moderately sized aggregates of plasma cells and atypical lymphocytes. Based on these findings, we made a diagnosis of sensorimotor neuropathy due to lymphoplasmacytic lymphoma, which corresponds to the clinical syndrome of WM. At 75 years of age, the patient found it difficult to walk during the month of February due to muscle weakness of his right leg, which subsequently spread to his left leg. In June, further laboratory tests showed the patient had normocytic anemia (Hb 7.0 g/dL, normal range: 13.4–17.6 g/dL), along with increases in his total protein (10.6 g/dL, normal range: 6.7–8.3 g/dL), soluble interleukin-2 receptor (2904 U/mL, normal range: 121–613 U/mL), IgG (4463 mg/dL, normal range: 870–1700 mg/dL), and IgM (3165 mg/dL, normal range: 32–190 mg/dL). Furthermore, anti-sulfated glucuronic acid paragloboside (SGPG) titer was normal, while the Hu, amphiphysin, CV2, PNNMA2 (Ma2/Ta), Ri, Yo, Hu, recoverin, SOX1, titin, zic4, GAD65, and Tr (DNER) antibodies were negative. After an exacerbation of WM was determined, chemotherapy with FRC therapy (fludarabine 30 mg orally on days 1–3; cyclophosphamide 250 mg orally on days 1–3, and rituximab 500 mg i.v. day 1) was administered for a total of five cycles, with a 4–5 week period between each cycle. At 76 years of age, although the patient’s hematological and serological results improved, he required the use of a wheelchair starting in April. In November, the patient was admitted to the hospital and underwent intravenous infusions of immunoglobulin on two occasions, although no response was noted except for dysphagia. At 77 years of age, muscle weakness developed in his arms in the month of March, especially on the right side. This subsequently worsened in conjunction with a loss of muscle mass. In addition, his voice became progressively softer and more hyponasal and he exhibited increased difficulty in swallowing food and liquids. During an examination, the deep-tendon reflexes in all of his extremities were classified as areflexia. The plantar responses were bilaterally equivocal. Brain MRI showed mild periventricular leukomalacia. Spinal magnetic resonance imaging (MRI) revealed mild flattening without abnormal intensity area in the spinal cord at the C4/5 level. Percutaneous gastrostomy was performed in September due to difficulties in drinking liquid. Furthermore, there was a gradual progression of his respiratory disturbance. The patient died of respiratory failure with aspiration pneumonia in October at 77 years of age, which was nearly 19 years after the original WM onset. There was no cognitive disturbance detected throughout his clinical course.

**PATHOLOGICAL FINDINGS**

The brain exhibited a normal weight (1190 g) with slight atrophy in the bilateral frontal lobes. The structures of the cerebellum, brain stem, and cranial nerves were all shown to have normal shapes. There were no malignant findings at the leptomeningeal, dura, and superior sagittal sinus. Routine staining with hematoxylin-eosin (HE) and Luxol fast blue (LFB) showed the presence of preserved neurons in the hippocampus and cerebral cortices. No degeneration of the pyramidal tract was detected. The motor neurons of the hypoglossal nuclei revealed mild degeneration. However, while other motor neurons for the oculomotor nerve, trochlear nerve, and the facial nerve nuclei were intact, the motor nucleus of the trigeminal nerve was not detected in the specimen. On immunostaining with a mouse monoclonal antibody against phosphorylated transactivation response DNA-binding protein of 43 kDa (TDP-43) (clone #PS409/410; CosmoBio, Tokyo, Japan; diluted 1:3000) were observed in the motor neurons of the hypoglossal nuclei with the exception for the oculomotor nerve, trochlear nerve, and the facial nerve nuclei. In addition, phosphorylated TDP-43-positive cytoplasmic

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inclusions were not detected in the neurons of the cerebrum and the hippocampal dentate gyrus.

The cervical and lumbar enlargements of the spinal cord were no longer macroscopically visible. There was atrophy of the anterior horn at all levels of the cervical spinal cord without myelin pallor of the pyramidal tracts, and there was marked loss and degeneration of motor neurons (Fig. 1A–C). Moreover, while the number of motor neurons was decreased throughout the entire level from the cervical to lumbar regions of the cord, astrocytosis was otherwise mild. Phosphorylated TDP-43-positive cytoplasmic inclusions were observed in the spinal and hypoglossal motor neurons as well as the astrocytes (Fig. 1D). Infiltrating inflammatory cells, which were positive with a mouse monoclonal antibody against the B cell marker CD20 (clone L26; Nichirei Biosciences, Tokyo, Japan; diluted 1:2) existed around the blood vessels of the spinal cord (Fig. 1E, F). There were no malignant cells confirmed within the spinal cord. However, there was marked degeneration of the gracilis on one side of the cervical spinal cord (Fig. 1A), and there were no Bunina bodies in the spinal motor neurons. Peripheral nerves from the lumbar ventral, dorsal roots, dorsal root ganglia, and lumbar plexus were also examined. There were diffuse infiltrations of inflammatory cells, mainly consisting of CD20-positive B cells as well as other type cells positive with a mouse monoclonal antibody against the plasma cell marker CD38 (clone vs38c; Dako, Glostrup, Denmark; diluted 1:1000), in the perivascular lesions of the peripheral nerves (Fig. 2A–D). There were no apparent lesions in the dorsal root ganglia. The number of macrophages and plasma cells in the bone marrow from the breastbone was increased. Blood cell phagocytosis by macrophages was observed in the bone marrow specimen. No malignant cells were observed. Grouping atrophy with small angular atrophy was detected in the iliopsoas muscle, which suggests there was a neurogenic change (Fig. 2E). Moreover, there were many plasma cells infiltrating the iliopsoas muscle (Fig. 2F).

DISCUSSION

We report a case of a 77-year-old man who developed WM with sensorimotor neuropathy. The early stages of the disease occurred at 58 years of age, with complications including muscle weakness that was not noted until the later part of the disease course, which was observed at the age of 75 years. Lower MND diagnosis was finally pathologically confirmed during the autopsy. In conjunction with the observed increase in the serum IgM and IgG, we also noted there was a gradual worsening of lower limb weakness along with a lack of effectiveness of chemotherapy and intravenous immunoglobulin without dysesthesia. Compared with typical pathological findings seen for amyotrophic lateral sclerosis (ALS), the present case exhibited marked loss of lower motor neurons along the whole spinal cord with only mild astrocytosis, and well-preserved pyramidal tracts. Chronic inflammatory cell infiltration may modify the progression of neuronal degeneration of the lower motor neurons.

Autopsy-proven MND associated with paraproteinemia of WM is quite rare. In a large case series, Gordon et al. analyzed 56 cases of MND with lymphoproliferative disease and demonstrated that 73% of the cases only reported lower motor neuron signs. However, this previous study only examined three postmortem patients, all of whom had clinical ALS. All of these cases showed loss of motor neurons in the spinal cord, brainstem, and motor cortex, with bilateral degeneration of the corticospinal tracts up to the medullary pyramids, which is consistent with ALS. Furthermore, one patient had widely disseminated Hodgkin’s disease, while another patient had WM with antibodies to SGPG. In addition, Jurici et al. reported an autopsy case of ALS with WM and anti-MAG monoclonal gammopathy. There was no invasion of malignant cells into the nervous system found in any of these cases. Therefore, these findings suggest that immunological factors may be related to the onset of ALS. In our case, there was exacerbation of the muscle weakness of the lower limbs along with a deterioration of the immunological findings, which included the progression of anemia and increases of both IgG and IgM. Neuronal loss in the anterior horn throughout the whole spinal cord was severe as compared to the interstitial mild gliosis. These facts are considered to be atypical for classical ALS. Furthermore, inflammatory cells were seen in the anterior and posterior roots of the cord without dorsal root ganglia and around the vessels of the spinal cord. In addition, these observations are also not consistent with the pathological findings for ALS.

Neurodegenerative disorders such as ALS and frontotemporal lobar degeneration exhibit TDP-43 proteinopathy as their primary histopathological feature. Furthermore, intracytoplasmic inclusions containing abnormal hyperphosphorylated and ubiquitinated TDP-43 are one of the pathological characteristics seen for ALS, with TDP-43 genetic mutations directly related to the onset of ALS. TDP-43 is a widely expressed DNA/RNA binding protein that plays an important role in the regulation of RNA metabolism in normal cells. It is unclear whether the selective motor neuron degeneration that characterizes ALS is caused by the disappearance of the nuclear TDP-43 and cytoplasmic accumulation, and if so, whether this intracytoplasmic TDP-43 inclusion leads to the acquisition of toxicity. Thus, although the mechanism responsible for generating TDP-43 cytoplasmic inclusions in the present case is unknown, we speculate that...
Fig. 1 Pathological findings in the cervical spinal cord. (A) A transverse axial section at C6 level is atrophic, particularly at the anterior horn. Both the lateral corticospinal tracts are intact. One side of the gracilis fasciculus shows myelin pallor. (B) Severe neuronal loss is observed at the anterior horn. (C) The anterior horn remarkably shows motor neuron atrophy and astrogliosis. (D) Phosphorylated TDP-43 immunoreactivity is detected in cytoplasmic inclusions of the motor neurons and astrocytes. (E) Inflammatory cell infiltrates are seen around the anterior spinal cord artery at C6 level. (F) In a serial section of (E), the infiltrating cells around the vessel are immunoreactive for CD20. LFB & HE stain (A-C), Immunostain (D, F), HE (E). Scale bars: 30 μm (A-D), 100 μm (E, F).

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Fig. 2  Pathological finding in the peripheral nervous system (A-D) and iliopsoas muscle (E, F). (A, B) In a posterior nerve root of the lumbar spinal cord, perivascular inflammatory cell infiltrates are seen. (C, D) The infiltrating cells in the posterior nerve root are immunoreactive for the B lymphocyte marker CD20 (C) or the plasma cell marker CD38 (D). (E, F) Iliopsoas muscle shows group atrophy with appearance of small angulated fibers (E) and infiltration of CD38-immunoreactive plasma cells (F). HE stain (A, B), Immunostain (B-D). Scale bars: 200 μm (A), 20 μm (B-D), 300 μm (E), 50 μm (F).
TDP-43 secondarily accumulated in the cytoplasmic inclusions in combination with an immunological mechanism or paraneoplastic factor due to WM or in an associated age-dependent manner. On the other hand, there is a possibility that lower MND coincidentally could have merged in the present WM case. A further analysis will need to be undertaken in order to elucidate the pathological mechanism of TDP-43 formation in WM.

In the 1970s, Schold et al. investigated 10 patients who developed lower MNDs with malignant lymphoma and proposed the cause of the disease was due to subacute motor neuronopathy. This disease was accompanied not only by the disappearance of the motor neurons of the anterior horn but also by the demyelination of the posterior funiculus. Subsequently, radiation myelopathy that selectively affects the anterior horn neurons was described as being a potential cause. In addition, these authors speculated that radiation myelopathy or an opportunistic infection could also be contributing factors. In contrast, Forsyth et al. reported finding both a decrease of motor neurons of the anterior horn and the degeneration of the funiculus in a prostate cancer patient, although this case was not treated by radiation. These authors speculated that these pathological findings could have been induced by the remote effect of the internal malignancy. In the present case, this patient did not undergo radiation therapy and did not exhibit any definitive findings of the infectious disease. Thus, this case might have been related to the vulnerability of the motor neurons with the remote effect related to the internal malignancy.

In conclusion, this case report presents data on a WM patient who developed sensorimotor neuropathy at an early stage of the disease, with lower MND subsequently occurring during the later stages of the disease course. Although the relationship between WM and lower MND is uncertain, we speculate that a paraneoplastic effect or immunological factors due to WM might enhance motor neuron death and degeneration of the posterior funiculus.

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DISCLOSURE

The authors declare no conflicts of interest for this article.