Predominant Sensory Ataxic Neuronopathy Showing Marked Improvement after Resection of a Thymoma Followed by Intravenous Immunoglobulin Therapy

Yasutaka Tajima, Yasunori Mito and Kazumasa Sudo

Abstract

A 64-year-old man was admitted to our hospital because of difficulty in walking and numbness in his lower extremities. Upon investigation, the patient was diagnosed as having predominant sensory ataxic neuronopathy associated with thymoma. Surgical resection of the thymoma followed by intravenous immunoglobulin therapy resulted in marked improvement of the patient’s clinical symptoms; therefore immunological mechanisms related to the presence of the thymoma were suspected to underlie the neuropathy in this patient. We did not find any previous reports of an association of sensory ataxic neuronopathy with thymoma, even after a thorough search of the literature.

Key words: paraneoplastic syndrome, sensory ataxic neuronopathy, thymoma, immunoglobulin

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Introduction

Thymoma is known to be associated with various neurological symptoms, including myasthenia gravis and neuro-myotonia, through immunological pathways (1). In the aforementioned conditions, autoantibodies such as anti-acetylcholine receptor antibodies (Ach-R) and anti-voltage gaited potassium channel (VGKC) antibodies are known to play pivotal roles (2-4). Herein, we present a case of predominant sensory ataxic neuronopathy associated with thymoma. Surgical resection of the thymoma followed by intravenous immunoglobulin therapy resulted in marked improvement of the patient’s clinical symptoms; therefore immunological mechanisms related to the presence of thymoma were suspected to underlie the nervous system involvement in this patient.

Case Report

A previously healthy 64-year-old man presented with a 3-month history of persistent numbness and tingling in the bilateral lower extremities. The symptoms began to ascend to the upper extremities, and the patient also began to perceive difficulty in walking. He was therefore admitted to our hospital for further examinations. He had no family history of neurological disorders, and his past medical history was not remarkable.

On admission, his body temperature was 36.5°C, and his blood pressure was 125/80 mmHg. Physical examination revealed no abnormalities. Neurologically, the deep tendon reflexes were sluggish, and the patient had glove-stocking type of sensory disturbance. The vibration and position sensations were markedly disturbed, especially in the lower extremities. The patient showed a markedly unsteady gait, and the Romberg sign was positive. Cranial nerve functions were intact, and no pathological reflexes were elicited. There were no signs of cerebellar disease. There was no evident muscle weakness. The patient did not have a history of bowel symptoms or bladder dysfunction. Blood chemistry was unremarkable, and serum tests for tumor markers such as CEA, CA19-9, NSE, and PSA were negative. The serum immunoglobulin levels were normal, and no M protein was detected. The serum test for anti-acetylcholine receptor antibody was negative, and no autoantibodies suggestive of collagen vascular diseases were detected either.
Table 1. Nerve Conduction Studies before (A) and after (B) the Treatments

<table>
<thead>
<tr>
<th></th>
<th>Motor Nerve</th>
<th>side</th>
<th>distal latency (ms)</th>
<th>conduction velocity (m/s)</th>
<th>amplitude (μV)</th>
</tr>
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<tbody>
<tr>
<td>A</td>
<td>Median nerve</td>
<td>right</td>
<td>6.6</td>
<td>87.9</td>
<td>8.8</td>
</tr>
<tr>
<td></td>
<td>Normal (CV42.0)</td>
<td>left</td>
<td>9.2</td>
<td>56.2</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>Tibial nerve</td>
<td>right</td>
<td>7.2</td>
<td>42.3</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>Normal (CV40.0)</td>
<td>left</td>
<td>7.2</td>
<td>43.5</td>
<td>5.2</td>
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<tr>
<td></td>
<td>Sural nerve</td>
<td>right</td>
<td>n.d.</td>
<td>n.d.</td>
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<td></td>
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<td>left</td>
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<tr>
<td>B</td>
<td>Median nerve</td>
<td>right</td>
<td>3.9</td>
<td>61.9</td>
<td>7.9</td>
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<tr>
<td></td>
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<td>left</td>
<td>4.3</td>
<td>54</td>
<td>11.2</td>
</tr>
<tr>
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<td>Tibial nerve</td>
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<td>42.5</td>
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<tr>
<td></td>
<td>Normal (CV42.0)</td>
<td>left</td>
<td>46.8</td>
<td>56</td>
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</table>

n.d.: not detected
CV: conduction velocity

Nerve conduction studies on admission revealed prolonged distal latency of the median, and tibial nerves bilaterally (Table 1). Motor nerve conduction velocities were spared; however, the amplitudes of the compound muscle action potentials stimulated by the tibial nerves were slightly reduced. No sensory nerve action potentials were detected in the median nerves. Sensory action potentials of sural nerves were detected; however, their amplitudes were slightly reduced. There was no evidence of conduction block. The test for somatosensory evoked potentials (two days after admission) demonstrated delayed N20 (32.15 ms) for the median nerve and delayed P36 (50.7 ms) for the tibial nerve (Fig. 1A, 1C). In addition, N11 and N13 were scarcely seen in the cervical cord, and no N20 was seen in the thoracic cord either. The patient refused sural nerve biopsy. CSF examination (four days after admission) revealed an elevated protein content (124 mg/dL) and a normal cell count (0.3/mm³). The intrathecal IgG level was elevated (10.20 mg/dL). Gadolinium-enhanced MRI (five days after admission) showed enhancement of the cauda equina (Fig. 2A, 2B). On the basis of these findings, the patient was diagnosed as having predominant sensory neuronopathy. Partial axonal degeneration and demyelination were considered. Spinal posterior columns also appeared to be involved. Electrophysiologically, the motor nerves were also found to be mildly affected. CT examinations (seven days after admission) revealed the presence of a mediastinal tumor (Fig. 2C). On the basis of these findings, the patient was diagnosed as having predominant sensory neuronopathy. Partial axonal degeneration and demyelination were considered. Spinal posterior columns also appeared to be involved. Electrophysiologically, the motor nerves were also found to be mildly affected. CT examinations (seven days after admission) revealed the presence of a mediastinal tumor (Fig. 2C). Ten days after admission, the patient was started on intravenous immunoglobulin (IVIG) therapy (0.4 g/kg for 5 days); however, no clinical improvement was noted.

Three weeks after admission, the patient received an extended thymectomy, and a well-encapsulated solid tumor was removed. Microscopic examination revealed a proliferation of spindle-shaped thymic epithelial cells and small lymphocytes without atypia. According to the World Health Organization (WHO) histological classification, the patient’s thymoma was classified as type AB (5). Infiltration of the tumor cells beyond the fibrous capsule was not seen. Two weeks after resection of the thymoma, the patient began to report a steadier gait and a slight improvement in the sensory disturbances. Since improvement of his neurological symptoms was gradual, and unsatisfactory, additional IVIG treatment was administered on the 45th hospital day, with the patient finally showing a significant improvement in his walking ability; the Romberg sign became negative.

The serum tests for anti-Hu antibody and anti-Yo antibodies, as well as those for anti-ganglioside antibodies and anti-VGKC antibodies, were negative. We could not measure the anti-CV2/CPRM-5 antibody in the serum. Re-examinations by spinal MRI and CSF could not be performed because of the patient’s refusal. Over the subsequent 2 years’ follow-up, the patient did not notice any signs of recurrence of neurological symptoms. The deep tendon reflexes were almost normal, and his walking ability improved. He noticed numbness of the finger and toe tips, but the intensity was much lower than previously experienced.

Nerve conduction studies after the treatments revealed improvement of the distal latencies of the median and tibial nerves (Table 1). The amplitudes of compound muscle action potentials by the tibial nerve stimulation increased. Sensory action potentials of the median nerves could be recorded. Results of the test for somatosensory evoked potentials (SEP) also lent support to the clinical improvement (Fig. 1B, 1D). The latency of N20 was 21.95 ms, and N11 and N13 were both easily detected in the median nerve stimulation. The latency of P36 improved from 51 ms to 46 ms, and the P36 was more clearly identified.

Discussion

In the present case, the possibility of the thymoma being a coincidental lesion could not be completely ruled out.
Figure 1. Tests for somatosensory evoked potentials in the median nerves (A) and tibial nerves (C) before the treatment. N20 was seen at 32.15 ms (A), and N11 and N13 could scarcely be seen (A). P36 was seen at 50.7 ms, and its amplitude was quite low (C). After the resection of the thymoma and repeat IVIG treatment, N20 was seen at 21.95 ms (B) and P36 was seen at 46 ms (D). N11 and N13 were more evident in the cervical cord (B), and N20 was more obvious in the thoracic cord (D).

Figure 2. MRI showing enhancement of the cauda equina (A: with DTPA, B: without DTPA). CT examinations revealed the presence of a mediastinal tumor that was later diagnosed histopathologically as a thymoma (C; arrow).
However, with additional IVIG treatment after resection of the thymoma, the patient showed a marked clinical improvement, and at the end of 24 months’ follow-up, no neurological deterioration was observed.

In general, sensory ataxic neuropathies are characterized by the loss of proprioceptive sensations and preservation of muscle strength. Pathological investigations demonstrate prominent neuronal cell loss of the dorsal root ganglia (DRG). Inflammatory cell infiltrates composed of CD8-positive T cells and CD68-positive macrophages into the DRGs are seen. CD20-positive B cells and macrophages are detected in the perivascular areas. There is also secondary Wallerian degeneration of the sensory nerves, dorsal roots, and dorsal columns within the spinal cord. This type of neuronopathy is sometimes associated with internal malignancies or collagen vascular diseases, and often poses difficulties in treatment (6).

In recent years, several onconeural antibodies have been identified in association with a variety of paraneoplastic neurological syndromes (PNS) (7-9). Among them, subacute sensory neuronopathy is classified as one of the classical PNS and has been seen to be frequently associated with small cell carcinoma of lung. In these cases, the serum levels of anti-Hu antibody and the recently identified anti-CV2/CRMP-5 antibodies have been well known to be correlated (9, 10). After 2 years’ follow-up, however, we saw no recurrence of the neurological symptoms and no evidence of lung carcinoma in the present case. The serum test for anti-Hu antibody was negative, whereas that for anti-CV2/CRMP-5 antibody could not be performed in this case. The major clinical symptoms and results of electrophysiological investigations in our case were consistent with those of PNS. Motor nerve conduction velocities were spared; however, the distal latencies were markedly prolonged. The frequency of F wave appearances was decreased. These findings could indicate the demyelinating event of the peripheral nerves. Sensory action potentials of the median nerves were not seen; thus, sensory nerves were also involved. The amplitudes of the action potentials increased after the successful treatment, which indicates axonal involvement too. The conduction time within the spinal cord was markedly improved after the treatment. This finding indicates the pathological involvement of the posterior column within the spinal cord. Some of the above-mentioned findings do not seem to be consistent with the diagnosis of sensory neuronopathy. In addition, although the clinical symptoms of this patient were more prominent in the lower extremities than in the upper extremities, sensory nerve conduction studies (NCS) showed that the median nerves were severely damaged, while the sural nerves were almost intact. Considering the spreading pattern during the course of the nervous system involvement, we speculated that neuronopathy and posterior column damages was dominant in the lower extremities, and that the damage of the peripheral nerves, especially that of the sensory nerves, occurred predominantly in the upper extremities. The exact mechanisms of this phenomenon remains unknown, but this may be partly attributed to the different distribution of the target antigens in the nervous system that were attacked by the disease-specific antibodies.

Graus et al have published the recommended diagnostic criteria for PNS (7). They describe that paraneoplastic sensory neuronopathy is not always an isolated syndrome, and that a neurological evaluation may demonstrate involvement of the motor nerves, peripheral autonomic nervous system, or different areas of the brain. That would seem to be true in the present case. On the other hand, MRI examinations did not reveal apparent spinal cord involvement, although gadolinium enhancement of the cauda equina, which has often been seen in chronic inflammatory demyelinating polyneuropathy (CIDP) (6), was recognized. That MRI finding looked quite characteristic in the present case. Demyelinating neuropathies are sometimes seen in lymphoproliferative disorders such as Hodgkin’s disease. Additionally, subacute/chronic sensorimotor neuropathy is known as one of the non-classical PNS. Some of these cases are known to exhibit a clinical course similar to CIDP, and it is plausible that common immunological mechanisms were also involved in the present case.

In 1996, Homorat et al first identified anti-CV2 antibody in a case of PNS (11). They analyzed 11 cases of PNS in detail and reported 2 cases of malignant lymphoepithelial thymoma. The neurological symptoms of those 2 cases were limbic encephalitis and myasthenia gravis with encephalopathy. In 2001, Yu et al analyzed 116 anti-CRMP-5 antibody-positive patients and identified 7 cases of thymoma (12). Among them, 3 patients had myasthenia gravis, and 3 had encephalitis, and 1 had systemic lupus erythematosus. In the report of Yu et al, 89 cases of the 116 CRMP-5 positive patients had lung carcinoma. The subtle differences between the target molecules of anti-CV2 antibody and anti-CRMP5 antibody have been previously discussed (13), but their expression patterns in cases of PNS were quite similar. The present patient did not show any evidence of central nervous system involvement or myasthenic syndromes. Even after a thorough search of the literature, we could not find any previous reports of the association of sensory ataxic neuronopathy with thymoma. The absence of any beneficial effect of the initial immunoglobulin administration, and the clinical improvement observed following the immunoglobulin treatment administered after the thymoma resection strongly suggest that the patient’s neuronopathy may have been related to the thymoma through immunological mechanisms.

More detailed investigations of this type of neuronopathy are necessary to identify the immunological mechanisms of thymoma and the neurological involvement.

References

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