Improvement of Anti-Hu-associated Paraneoplastic Sensory Neuropathy after Chemoradiotherapy in a Small Cell Lung Cancer Patient


Abstract

A 66-year-old man developed progressive painful dysesthesia in his hands and feet over 3 months. His vibration sense was impaired and sensory nerve action potentials of the limbs were not evoked. Biopsy of the peroneal nerve revealed sensory neuropathy. Positive anti-Hu antibody facilitated delineation of a right hilar mass and a metastatic lymph node in thoracic CT scan. He was diagnosed as small cell lung cancer associated with paraneoplastic sensory neuropathy. A complete response was achieved through chemotherapy (carboplatin and etoposide) and subsequent radiation therapy. Notably, his neurological conditions, although not changed during the hospitalization, gradually improved afterwards.

(Key words: paraneoplastic syndrome, paraneoplastic neurological syndrome, anti-Hu antibody)

Introduction

Subacute sensory neuropathy is often associated with malignant tumors, most of which are small cell lung cancer (SCLC) (1). It is also called paraneoplastic sensory neuropathy (PSN). This neuronal disorder is characterized by the presence of antibody which recognizes autoantigens present in nuclei of neuronal cells. The antibody, designated anti-Hu (HuAb), was considered to be raised against the same antigens present in SCLC (2-4). Notably, SCLC-associated paraneoplastic syndromes including subacute sensory neuropathy frequently precede the detection of tumors (5), and SCLC with high titers of HuAb tends to respond well to conventional chemotherapy, leading to favorable survival of patients (6). However, the improvement of PSN is generally not observed (5).

Here, we present a case of SCLC preceded by HuAb-associated PSN. Progression of PSN over 3 months and detection of HuAb lead to the search for SCLC. Three courses of combination chemotherapy and 20 Gy of radiation not only induced a complete remission of the tumor, but later promoted gradual recovery of his neurological deficit.

Case Report

A 66-year-old man developed progressive painful dysesthesia in the distal limbs for 3 months. The patient started to feel discomfort in the distal fingers late in July 1999. This symptom was progressive; one week later, both hands were completely numb. Impaired sensation also spread from his toes to each entire foot. Late in August, his gait was disturbed because of foot pain. He was admitted to our hospital late in October. The patient was a 120 pack per year smoker, and had a history of tuberculosis pleuritis at the age of 10 years and a 25-year treatment history for hypertension, but no past history of alcoholism and no familial history of neuropathy.

Physical examinations showed no abnormalities except for neuromuscular findings. Neurological examination displayed dysesthesia and hyperalgesia in both hands and feet. Vibration sense was moderately reduced. Pain and touch sensation was also impaired but to a lesser degree. Deep tendon reflexes were moderately decreased in all limbs. Muscle strength in the upper and lower limbs was mildly weakened. Shellong test was positive (136/76 mmHg in the supine position, whereas 85/49 mmHg in the standing position). Dysuria was seen without increased frequency of urination or prostatic hypertrophy.

Laboratory examination revealed slight decreases in serum Na (135 mEq/l) and creatine kinase (25 U/l). Protein in cerebrospinal fluid was elevated to 115 mg/dl. No abnormal findings were seen in studies for infection, immunology, or endocrinology. Multiple cerebral lacunar infarctions in the white matter of the brain were detected by magnetic resonance imaging.

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matter and mild cerebellar atrophy were seen in magnetic resonance imaging of the brain. No apparent tumor was detected on a chest X-ray film except for parenchymal linear shadows and minimal pleural calcification in the left lobe, which were compatible with old tuberculosis (Fig. 1). Neurophysiological examinations displayed absent action potentials in the median, tibial and sural sensory nerves, whereas only minimal reduction of conduction velocity was observed in motor nerves, indicating sensory neuropathy (Table 1, October 28, 1999). Electromyography (EMG) also exhibited the presence of neurogenic changes with moderate polyphasic motor action potentials with long duration in the leg and arm muscles. A reduction in the number of myelinated fibers and the presence of myelin debris were obvious as seen in a biopsy specimen of the lateral cutaneous branch of the superficial peroneal nerve (Fig. 2). Thinly myelinated or demyelinated fibers were rarely seen. There was no evidence of infiltration of inflammatory cells or vasculitis. In a teased fiber preparation, 78% of fibers presented late stage of axonal degeneration, while the left peroneus brevis muscle revealed no significant abnormalities.

From these results, the patient was suspected to have sub-

![Figure 1](image1.png)

**Figure 1.** Linear shadows and pleural calcification in the left middle lung field are seen, but no apparent tumor is obvious in a chest X-ray film on admission.

![Figure 2](image2.png)

**Figure 2.** (A) An epon-embedded semi-thin section of the lateral cutaneous branch of the superficial peroneal nerve showing moderate reduction in the number of myelinated fibers (thionin stain, ×180, Bar, 100 μm). (B) At the higher magnification, many myelin ovoids (myelin breakdown after axonal degeneration) are seen (×900, Bar, 20 μm).

**Table 1. Nerve Conduction Data**

<table>
<thead>
<tr>
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<th>October 28, 1999</th>
<th>April 4, 2000</th>
<th>October 20, 2000</th>
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<tr>
<td>Sensory nerve conduction velocity (m/s)</td>
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<td></td>
<td></td>
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<tr>
<td>Right median (W-E)</td>
<td>NE</td>
<td>NE</td>
<td>38.3*</td>
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<tr>
<td>Right tibial (A-K)</td>
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<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Right sural (A-K)</td>
<td>NE</td>
<td>NE</td>
<td>34.9</td>
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<tr>
<td>Motor nerve conduction velocity (m/s)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Right median (W-E)</td>
<td>43.7</td>
<td>44.9</td>
<td>45.5</td>
</tr>
<tr>
<td>Right tibial (A-K)</td>
<td>34.0</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
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acute sensory neuropathy, possibly due to the presence of a latent malignant tumor. In fact, HuAb turned out to be positive and gastrin-releasing peptide precursor (pro-GRP) was elevated to 82.5 pg/ml (normal range <46 pg/ml) in the serum. Gallium scintigraphy was performed to survey the whole body, and abnormal hot spots were discovered at the right hilus of the lung and the right supraclavicular region. Thoracic computerized tomography (CT) scan revealed a primary tumor in the right hilus of the lung (ϕ 2 cm) and a metastatic supraclavicular lymph node (ϕ 1 cm) (Fig. 3). Histological diagnosis of SCLC was made through the supraclavicular lymph node biopsy. Eventually, the patient was clinically diagnosed as paraneoplastic sensory neuropathy with a limited disease of SCLC (clinical T1N3M0, stage IIIB). Combination chemotherapy (carboplatin and etoposide) with subsequent radiation therapy was administered. Complete tumor regression was observed and the serum pro-GRP level returned to within the normal limits, while his neurological symptoms remained stable (Table 1, April 4, 2000). After three courses of chemotherapy and 20 Gy of radiotherapy, the patient rejected further treatment because his neurological conditions started to improve gradually. In October 2000, he still had mild paresthesia but felt little pain in his hands and feet with no evidence of tumor recurrence. Vibration, touch, and pain sensation were also slightly ameliorated, while the decrease of deep tendon reflexes, orthostatic hypotension and mild dysuria were persistent. Recovery of action potentials in the median and sural sensory nerves was confirmed in neurophysiological examinations (Table 1, October 20, 2000). HuAb was still positive in the serum at this point, although its titer was not examined.

Discussion

Paraneoplastic neurological syndrome including PSN and Lambert-Eaton myasthenic syndrome (LEMS) often precedes the detection of malignant tumors, and is characterized by the presence of autoantibodies against neuronal tissues. These antibodies, such as anti-Hu (HuAb) and anti-voltage-gated calcium channel (VGCC), are considered to be raised against antigens present in tumor cells and cross-react with normal neural cells (7). HuAb is a polyclonal complement-fixing IgG directed against RNA-binding proteins of 35 to 40 kD, which are concentrated in the nuclei of neurons of the central and peripheral nervous system (8, 9). It was reported that 80% of malignant tumors presenting HuAb-positive PSN were SCLC (5, 10), and that 80% of HuAb-associated PSN preceded the clinical diagnosis of malignant tumor (5). Although HuAb is a useful marker for PSN, there is no evidence that this antibody directly damages tumor cells or normal neural cells. It is likely that T-cell-mediated cytotoxicity is also involved in the progression of PSN (11). It was also reported that 95% of SCLC patients with HuAb-associated PSN had limited diseases within the chest (5), and that the presence of HuAb was an independent predictor for a complete response (6). Even spontaneous regression of SCLC with HuAb-positive PSN was reported elsewhere (12). Dalmau et al suggested that T-cell-mediated mechanisms may have contributed to tumor rejection in these cases (7). Notably, despite the good response of tumors to therapy and favorable survival of patients, improvement of PSN is rather rare (5). This is in contrast to LEMS, which tends to improve in response to therapy probably because neuronal cell bodies are spared in this syndrome (13). Although prednisolone, azathioprine, immunoglobulin or plasmapheresis have been tried, these have not proved effective for most PSN patients (14).

The patient in this report presented with marked abnormalities in sensory nerves in contrast to the minimal change in motor nerve function. Pathological examination indicated sensory neuropathy. Since no evidence supported malnutrition, collagen diseases, vasculitis, endocrinological abnormalities or metabolic disorders, PSN was suspected. Positive HuAb and elevation of pro-GRP in the serum indicated the presence of a latent malignant neoplasm. Although no abnormal nodules were detected on the chest X-ray, a limited disease of SCLC was disclosed by thoracic CT scan. Complete remission of the tumor was achieved through chemoradiotherapy, but the PSN was persistent and discouraged the patient from accepting further radiation or another course of chemotherapy. It is noteworthy, however, that the PSN started to be gradually ameliorated 1 month after the chemotherapy, and further 5 months later, his painful dysesthesia had almost disappeared without any im-

Figure 3. Thoracic CT scan showed a primary tumor in the right hilus of the lung (the arrow in the lower panel) and a metastatic supraclavicular lymph node (the arrow in the upper panel).
munosuppressive therapy or plasmapheresis. Possibly, the dorsal ganglion neurons might have been relatively spared at the onset of therapy in this patient.

Several mechanisms accounting for this neurological improvement are conceivable. First, complete remission of the tumor may have lead to a recession of cytotoxic T-cells. One report suggested that complete response of the tumor to therapy was the best predictor to arrest the evolution of the neurological dysfunction in HuAb-associated paraneoplastic encephalomyelitis including PSN (15). Although serum HuAb in our patient was still positive when action potentials in the sensory nerves reappeared, no evidence that the HuAb directly damages neural cells has been obtained. Moreover, correlation between serum titers of HuAb and neurological course has not been often seen (16). Second, anti-tumor drugs may have exerted an immunosuppressive effect on the sensory nerves. Recently, Keime-Guibert et al treated patients with PSN and paraneoplastic cerebellar degeneration with a combination of immunosuppressive agents, and reported that vigorous immunosuppressive therapy was effective for patients who were not severely disabled at the onset of treatment (16). They speculated that the lack of a blood-nerve barrier at the level of the dorsal root ganglia could facilitate the entry and action of immunosuppressors. Finally, the improvement of PSN in our patient might be spontaneous, as reported before (17). This is unlikely, however, because his neurological symptoms were clearly progressing in the month preceding the onset of the antineoplastic therapy.

In summary, we presented HuAb-associated subacute sensory neuropathy in a patient with SCLC. Although serum HuAb was still positive when action potentials in the sensory nerves reappeared, no evidence that the HuAb directly damages neural cells has been obtained. Moreover, correlation between serum titers of HuAb and neurological course has not been often seen (16). Second, anti-tumor drugs may have exerted an immunosuppressive effect on the sensory nerves. Recently, Keime-Guibert et al treated patients with PSN and paraneoplastic cerebellar degeneration with a combination of immunosuppressive agents, and reported that vigorous immunosuppressive therapy was effective for patients who were not severely disabled at the onset of treatment (16). They speculated that the lack of a blood-nerve barrier at the level of the dorsal root ganglia could facilitate the entry and action of immunosuppressors. Finally, the improvement of PSN in our patient might be spontaneous, as reported before (17). This is unlikely, however, because his neurological symptoms were clearly progressing in the month preceding the onset of the antineoplastic therapy.

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References