

Brachial Diparesis due to Motor Neuronopathy as One of the Predominant Presenting Signs of Occult Small Cell Lung Carcinoma

Sefik Evren Erdener, Atay Vural, Cagri Mesut Temucin, Sevim Erdem Ozdamar, Gulay Nurlu, Kubilay Varli and Nese Dericioglu

Abstract

Sensory neuronopathy is a well-established presentation in paraneoplastic neurological syndromes that is mostly associated with small cell lung cancer and anti-Hu antibodies. Motor neuronopathy, on the other hand, is an extremely rare observation in this syndrome. A 56-year-old man presented with asymmetric brachial diparesis and sensory ataxia. Electrophysiological studies revealed sensory ganglionopathy and progressive anterior horn degeneration in cervical segments. Small cell lung carcinoma with associated anti-Hu antibodies was later diagnosed. The patient did not improve despite the administration of steroids and chemotherapy. Paraneoplastic syndromes may exceptionally present with a bilateral arm weakness. Cases accompanied by sensory ganglionopathy should therefore be promptly investigated for any underlying malignancy.

Key words: small cell lung cancer, paraneoplastic, anti-Hu, motor neuronopathy

(Intern Med 55: 1641-1643, 2016)

(DOI: 10.2169/internalmedicine.55.4888)

Introduction

Paraneoplastic neurological syndromes (PNS) are remote effects of cancer that involve the central and/or peripheral nervous system (1). Small cell lung carcinoma (SCLC) is the most common malignancy associated with PNS and is most commonly associated with anti-Hu antibodies. Patients often present with sensory symptoms such as numbness, paresthesia or pain involving the limbs (2). The muscle strength is generally preserved or only mildly decreased. We herein present a rare case of SCLC in which brachial diparesis was one of the predominant neurological findings.

Case Report

A 56-year-old man with a history of heavy smoking complained of dysesthesia in both arms and legs for the previous four months, followed later by feelings of weakness in both arms. A neurological examination revealed predominantly proximal and asymmetrical motor deficits in the upper ex-

tremities [Medical Research Council scores (right/left, over 5): shoulder abduction 3-/2, forearm flexion 4/1, forearm extension 4/3+, wrist flexion 5-/4+, wrist extension 5-/5-], without a motor deficit in the lower limbs. There was hypoesthesia in the distal left upper and both lower extremities. Vibration and position sense were decreased in both the distal lower extremities and in the distal left upper extremity. Deep tendon reflexes could not be elicited. There were no pyramidal signs. Ataxia could not be reliably evaluated in the upper extremities because of motor deficits, but the patient had a mildly ataxic and broad-based gait. The result of Romberg's test was positive.

The patient's blood test results were unremarkable. The results of a cerebrospinal fluid (CSF) examination were normal, except for positive oligoclonal bands. The results of a magnetic resonance (MR) investigation of the cervical spinal cord were also normal, ruling out other etiologies such as myelopathy or radiculopathy in the C5-6 region.

In initial nerve conduction studies, no sensory potentials could be elicited bilaterally in the upper and lower extremities. Compound muscle action potentials (CMAP) were nor-

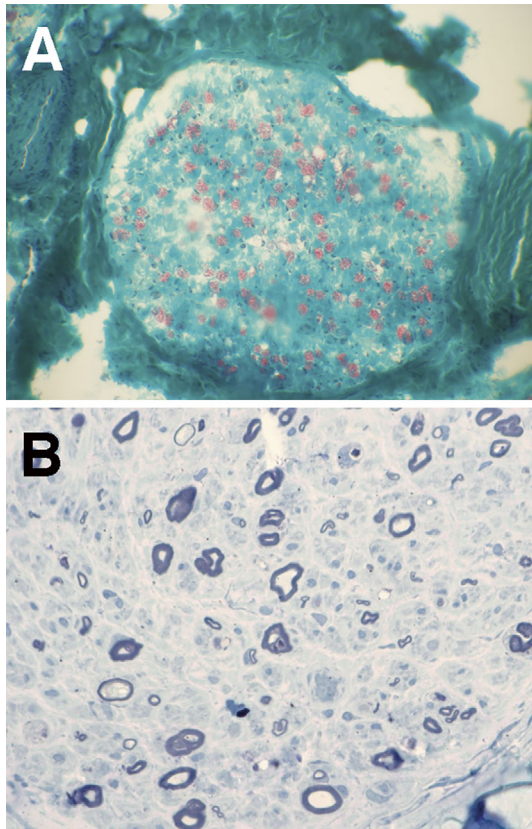


Figure 1. Sural nerve biopsy findings. (A) The decreased density of nerve fibers seen by Modified Gomori Trichrome staining is not accompanied by a vasculitic inflammatory reaction. (B) Epoxy-resin-embedded semi-thin plastic sections reveal moderate fiber loss with active axonal degeneration. No axonal sprouts suggesting regeneration are seen.

mal in the lower extremities, but were mildly decreased in the upper extremities. EMG findings demonstrated fibrillation potentials and positive sharp waves in the left deltoid, biceps brachii, C5-6 paraspinal and infraspinatus muscles, while the proximal and distal muscles in the right upper extremity and both lower extremities were normal (Supplementary material 1, 2). A widespread lack of sensory potentials and the presence of denervation potentials in a segmental distribution were consistent with sensory ganglionopathy and anterior horn degeneration in the left C5-C8 and T1 segments. A sural nerve biopsy revealed severe and active axonal degeneration (Fig. 1). As sensory ganglionopathy could be associated with paraneoplastic processes, the patient underwent a radiological screening for malignancies. Abdominal computerized tomography (CT) and scrotal ultrasonography results were normal, but thorax CT revealed subcarinal and paraesophageal lymphadenopathies. Tumor markers (including CA 15-3, CA 125, CA 19-9, carcinoembryonic antigen, lactate dehydrogenase, beta-2-microglobulin and prostate-specific antigen) were within normal limits. The patient's serum was also tested for paraneoplastic anti-neuronal antibodies, and a high titer (i.e., +++: the highest possible level by semi-quantitative techniques) of anti-Hu antibodies was detected by a semi-quantitative immunofluo-

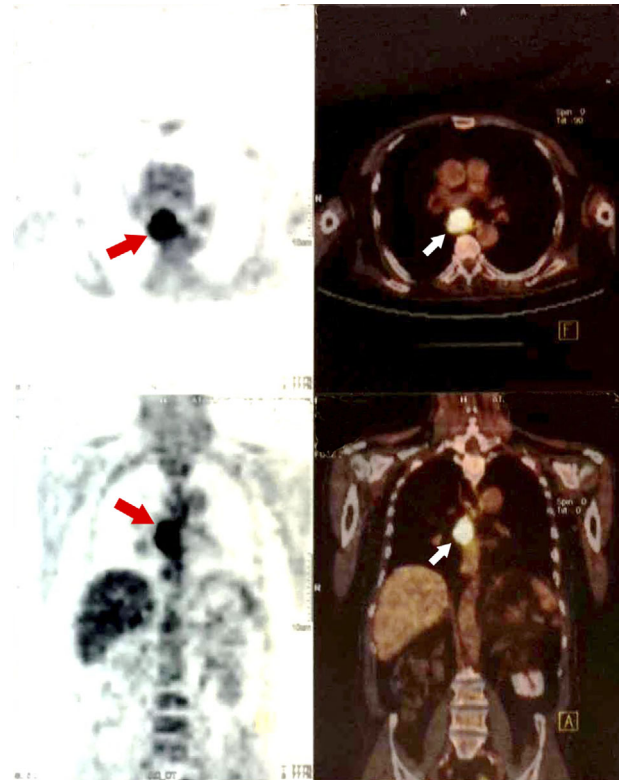


Figure 2. Increased fluorodeoxyglucose uptake in paraesophageal lymph nodes (arrows) is notable in axial and coronal plane images from a PET-CT study.

rescence antibody assay. Whole-body positron emission tomography (PET)-CT demonstrated a significant increase in the fluorodeoxyglucose signal in paraesophageal lymph nodes (Fig. 2). A bronchoscopic aspiration of the enlarged lymph nodes confirmed the presence of SCLC. The patient was started on intravenous methylprednisolone for five days, followed by an oral maintenance dose of 1 mg/kg. He was also put on cisplatin and etoposide chemotherapy.

Repeat thorax CT four months after the diagnosis and while receiving chemotherapy showed the resolution of the mediastinal lymphadenopathies with no parenchymal malignant tissue in the lungs. However, the patient's EMG at that time demonstrated a more pronounced decrease in CMAP amplitudes in the median and ulnar nerves bilaterally, as well as the presence of denervation potentials and polyphasic motor unit potentials in the left and right upper extremities proximally and distally (Supplementary material 1, 2). The patient's neurological status did not improve despite the medical treatment. There was no prominent clinical worsening either, and he did not develop motor deficit in the lower extremities up until his death at another institution, 18 months after the diagnosis.

Discussion

Our patient's clinical and laboratory findings comply with the suggested diagnostic criteria for acquired sensory neuropathies (3) with an asymmetrical distribution of sensory

loss at onset, sensory loss not being restricted to the lower limbs and more than one sensory nerve action potential being absent in the upper limbs, along with positive anti-Hu antibodies. The initial asymmetrical and segmental distribution of denervation potentials in EMG suggested motor neuronopathy rather than neuropathy.

This case demonstrates that, besides sensory symptoms, a significant motor deficit may also develop in anti-Hu-positive SCLC patients. In PNS, the symptoms usually consist of malignant inflammatory sensory polyganglioneuropathy, gastrointestinal dysmotility, autonomic neuropathy and limbic encephalitis (2). A motor neuron dysfunction is extremely rare as a PNS sign and has been reported in several patients with PNS and anti-Hu antibodies (4), two patients with SCLC and anti-neuronal antibodies (5) and three patients with motor neuron disease and other cancers (6) in three different studies. Apart from these series, two relevant reports of cases with lower motor neuron disease and anti-Hu antibodies have been published (7, 8). Similar to our patient, in both cases, motor weakness remained confined to the upper extremities and, histologically, anterior horn cell degeneration in the cervical region seemed to be more pronounced than at lumbar levels (8), possibly indicating an as-yet-undefined cause of susceptibility in this region of the spinal cord.

Anti-Hu antibodies are polyclonal IgG autoantibodies directed against 35-40-kDa proteins expressed in the nuclei of neurons and malignant cells. They cross-react with the nervous system tissues, leading to a humoral and T-cell-mediated immune response (9). Postmortem examinations of the spinal cord in three patients in the aforementioned studies revealed the marked depletion of anterior horn cells (6, 8), with inflammatory infiltrates (6). Although anti-Hu antibodies stain the nuclei of all neurons of the brain, spinal cord and dorsal root ganglia in a diffuse homogeneous manner (8), it is not clear why sensory polyganglioneuropathy predominates over motor neuronopathy. Differences in blood-nerve and blood-brain barriers may lead to an increased susceptibility of dorsal root ganglia compared with that of anterior horn cells, as suggested previously (10).

The outcome of patients with paraneoplastic neuronopathy is generally poor (4, 7, 8, 11). The ineffectiveness of various immunosuppressive therapies has been explained in part by

the synthesis of paraneoplastic antibodies in the central nervous system (12), and the intranuclear location of the relevant Hu-family RNA-binding protein. Further studies are needed to demonstrate the exact frequency of motor neuron involvement in the PNS and its underlying pathophysiology.

The authors state that they have no Conflict of Interest (COI).

References

1. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol, Neurosurg Psychiatry* **75**: 1135-1140, 2004.
2. Camdessanché JP, Antoine JC, Honnorat J, et al. Paraneoplastic peripheral neuropathy associated with anti-Hu antibodies. A clinical and electrophysiological study of 20 patients. *Brain* **125**: 166-175, 2002.
3. Camdessanché JP, Jousserand G, Ferraud K, et al. The pattern and diagnostic criteria of sensory neuronopathy: a case-control study. *Brain* **132**: 1723-1733, 2009.
4. Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. *Medicine (Baltimore)* **71**: 59-72, 1992.
5. Anderson NE, Rosenblum MK, Graus F, Wiley RG, Posner JB. Autoantibodies in paraneoplastic syndromes associated with small-cell lung cancer. *Neurology* **38**: 1391-1398, 1988.
6. Forsyth PA, Dalmau J, Graus F, Cwik V, Rosenblum MK, Posner JB. Motor neuron syndromes in cancer patients. *Ann Neurol* **41**: 722-730, 1997.
7. Lee JI, Macht S, Albrecht P, Hartung HP, Goebels N. Brachial amyotrophic diparesis associated with anti-Hu positive anterior horn cell disease and autonomic disorder. *J Neurol* **260**: 301-302, 2013.
8. Verma A, Berger JR, Snodgrass S, Petito C. Motor neuron disease: a paraneoplastic process associated with anti-Hu antibody and small-cell lung carcinoma. *Ann Neurol* **40**: 112-116, 1996.
9. Voltz R. Paraneoplastic neurologic autoimmune diseases. *Nervenarzt* **73**: 909-929, 2002 (in German, Abstract in English).
10. Elrington GM, Murray NM, Spiro SG, Newsom-Davis J. Neurological paraneoplastic syndromes in patients with small cell lung cancer. A prospective survey of 150 patients. *J Neurol Neurosurg Psychiatry* **54**: 764-767, 1991.
11. Vedeler CA, Antoine JC, Giometto B, et al. Management of paraneoplastic neurological syndromes: report of an EFNS Task Force. *Eur J Neurol* **13**: 682-690, 2006.
12. Furneaux HF, Reich L, Posner JB. Autoantibody synthesis in the central nervous system of patients with paraneoplastic syndromes. *Neurology* **40**: 1085-1091, 1990.