

# Anti-Hu Antibody-associated Paraneoplastic Neurological Syndrome Showing Peripheral Neuropathy and Atypical Multifocal Brain Lesions

Makoto Shibata<sup>1</sup>, Megumi Uchida<sup>2</sup>, Setsuki Tsukagoshi<sup>1</sup>, Koichi Yamaguchi<sup>2</sup>,  
Aya Yamaguchi<sup>2</sup>, Natsumi Furuta<sup>1</sup>, Kouki Makioka<sup>1</sup>, Toshitaka Maeno<sup>2</sup>,  
Yukio Fujita<sup>1</sup>, Masahiko Kurabayashi<sup>2</sup> and Yoshio Ikeda<sup>1</sup>

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## Abstract

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A 64-year-old Japanese woman presented with a three-month history of progressive numbness and weakness of the lower extremities. A neurological examination and nerve conduction study indicated sensorimotor polyneuropathy. Since the serum anti-Hu antibody titer was remarkably elevated, paraneoplastic neurological syndrome was highly suspected. A thoracoscopic biopsy of the hilar lymph nodes, in which <sup>18</sup>F-fluorodeoxyglucose uptake was obviously increased, revealed pathological findings for small-cell lung cancer (SCLC). Subsequently, the patient presented with generalized tonic-clonic seizures, and cerebral MRI showed reversible multifocal brain lesions, considered to reflect paraneoplastic encephalopathy. After two courses of chemotherapy for SCLC, the brain lesions totally disappeared.

**Key words:** paraneoplastic neurological syndrome (PNS), anti-Hu antibody, small-cell lung cancer (SCLC), peripheral neuropathy, cauda equina enhancement, encephalopathy

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## Introduction

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Paraneoplastic neurological syndrome (PNS) is a rare disorder caused by the remote effects of the underlying neoplasm and may affect any level of the neurological system (1, 2). Anti-Hu antibodies, also known as ANNA-1 (anti-neuronal nuclear autoantibodies type 1), are well-known anti-neuronal antibodies often associated with small-cell lung cancer (SCLC) (3). Anti-Hu antibodies can cause PNS, including sensory neuropathy, cerebellar ataxia and limbic encephalitis (3-5). We herein report a case of PNS with an elevated serum anti-Hu antibody titer showing peripheral neuropathy and encephalopathy. This case involved characteristic multifocal brain lesions on MRI. Very interestingly, the cerebral lesions disappeared after two courses of chemotherapy against SCLC.

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## Case Report

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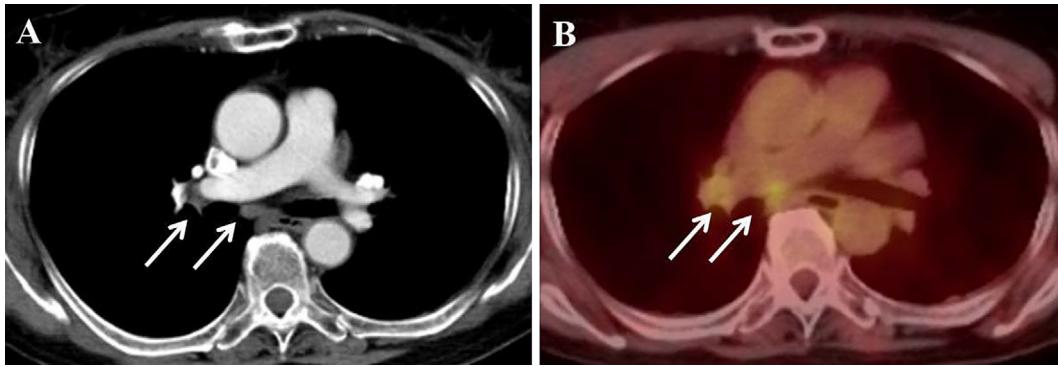
A 64-year-old Japanese woman presented with a three-month history of progressive numbness and weakness originating from the left lower extremity. Her symptoms gradually progressed to all extremities, and her walking was subsequently impaired. A neurological examination disclosed remarkable atrophy and weakness, predominantly in the lower extremities. The tendon reflexes were hyporeactive for the biceps brachii, brachioradialis and triceps brachii reflexes and absent for both the patellar and Achilles reflexes. Babinski's reflex was negative bilaterally, and Lasegue's sign was positive bilaterally. A sensory examination showed mild numbness of the anterior surface on both thighs, and superficial and deep sensations were diminished in all distal extremities. Laboratory tests, including a complete blood

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<sup>1</sup>Department of Neurology, Gunma University Graduate School of Medicine, Japan and <sup>2</sup>Department of Respiratory Medicine, Gunma University Graduate School of Medicine, Japan

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Correspondence to Dr. Yoshio Ikeda, ikeday006@gunma-u.ac.jp



**Figure 1.** Thoracic CT and FDG-PET findings. (A) Thoracic CT showed unenhanced small lymphadenopathy in the right hilum and subtracheal bifurcation (arrows), although the primary tumor of SCLC was not identified in the bilateral lung fields. (B) FDG-PET images showed increased uptake in these lymph nodes (arrows).

cell count and biochemistry, were normal. The serum pro-gastrin-releasing peptide (Pro-GRP) level showed pathological elevation at 93.5 pg/mL, while the serum anti-Hu antibody titer showed remarkable elevation at 1:122,880. A cerebrospinal fluid (CSF) examination disclosed a slight increase in the number of mononuclear cells ( $8/\text{mm}^3$ ) and an elevated level of total protein (187 mg/dL). In addition, the CSF  $\beta_2$ -microglobulin level was also elevated (5.70 mg/L), while the serum  $\beta_2$ -microglobulin level was normal (1.40 mg/L). CSF cytology revealed no atypical cells. Nerve conduction studies showed reduced amplitudes of the compound muscle action potentials in the peroneal and tibial nerves and the absence of sensory nerve action potentials in the median, ulnar and sural nerves, although no obvious slowing of the conduction velocity or conduction block were observed. Thoracic CT demonstrated unenhanced lymphadenopathy in the right hilum and subtracheal bifurcation (Fig. 1A).  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) showed an increased uptake in these lymph nodes (Fig. 1B). Additionally, gadolinium (Gd)-enhanced lumbar MRI demonstrated remarkable enhancement of the cauda equina (Fig. 2A, B), although FDG-PET showed no accumulation in this area. Cerebral MRI performed on admission revealed high signal intensity around the periventricular area (Fig. 2E). Nine years before admission, the patient had incidentally received a cerebral MRI examination due to a head injury. Notably, the periventricular white matter lesions were already present to the same degree as that seen on MRI performed on admission. Therefore, these lesions were thought to be due to chronic cerebral ischemia.

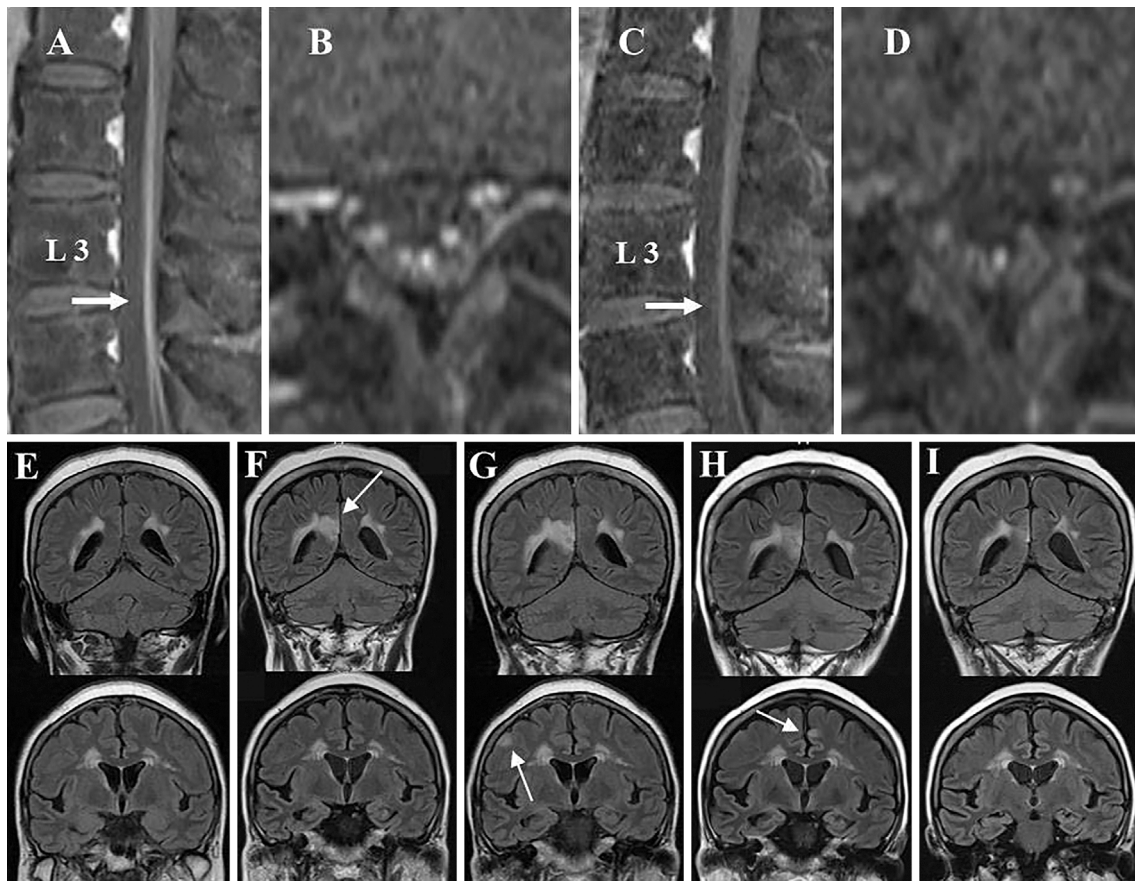
The patient was initially treated with high-dose intravenous immunoglobulin (IVIg) therapy, which resulted in a slight improvement in the numbness and weakness. However, after the IVIg therapy, the Gd-enhancement of the cauda equina dramatically decreased (Fig. 2C, D), which indicated tumor invasion to be less likely. Since the serum anti-Hu antibody titer was remarkably elevated, PNS associated with SCLC was suspected. A subsequent thoracoscopic

biopsy of the lymph nodes, in which  $^{18}\text{F}$ -FDG was accumulated, revealed pathological findings for SCLC. On day 82, the second cerebral MRI examination showed a new asymptomatic high-signal lesion in the right posterior cingulate cortex (Fig. 2F). Gd-enhanced MRI showed slight superficial enhancement, which is an atypical finding for brain metastasis. Meanwhile, magnetic resonance spectroscopy showed no signs of malignancy. On day 87, the patient presented with generalized tonic-clonic seizures and was started on treatment with anti-epileptic drugs. On day 88, the first course of chemotherapy (cisplatin and etoposide) against SCLC was started. However, on day 93, another high-signal lesion appeared in the right prefrontal cortex (Fig. 2G). On day 109, the signal intensity of these two lesions was diminished, although a new lesion further appeared in the left medial parietal cortex (Fig. 2H). On day 132, the patient was treated according to the second chemotherapy protocol (cisplatin and irinotecan). On day 134, the above mentioned lesions totally disappeared (Fig. 2I). Although the brain lesions resolved, the muscle atrophy and weakness in the limbs did not improve.

## Discussion

In a previous report reviewing 200 patients with anti-Hu antibody-associated paraneoplastic encephalomyelitis (PEM), sensorimotor neuropathy was present in 4.5% of the cases at the time of PEM diagnosis (4). An improvement or stabilization of the PEM was observed in 37.5% of the patients who received anti-cancer chemotherapy with or without immune-modulating therapies, compared to 20.6% of cases treated with immune-modulating therapy only. Since we were able to start anti-cancer chemotherapy against SCLC immediately after the multifocal brain lesions appeared in the current case, the patient's encephalopathy improved dramatically before resulting in irreversible disease.

There are a few reports of cases of PNS associated with Gd-enhancement of the cauda equina (6-8); however, positive results for anti-Hu antibodies were not confirmed in



**Figure 2.** Spinal and cerebral MRI findings. (A and B) Gadolinium-enhanced T1-weighted images showed remarkable enhancement of the cauda equina in the sagittal and axial views. (C and D) After intravenous immunoglobulin therapy, the enhancement of the cauda equina decreased in the respective views on day 59. The arrows in A and C indicate the level of the axial plane. (E) Two coronal planes on fluid-attenuated inversion recovery (FLAIR) images obtained on admission showed high signal intensity around the periventricular area. (F) On day 82, a coronal FLAIR image showed a new asymptomatic high-signal lesion in the right posterior cingulate cortex (arrow). (G) On day 93, another high-signal lesion appeared in the right prefrontal cortex (arrow). (H) On day 109, the two high-signal lesions were diminished, although a new lesion appeared in the left medial prefrontal cortex (arrow). (I) On day 134, the above mentioned lesions disappeared after two courses of chemotherapy for small-cell lung cancer.

these cases. Although IVIg therapy did not successfully improve the current patient's neurological symptom, the Gd-enhancement of the cauda equina improved dramatically. This finding may be due to a break in the blood-nerve barrier secondary to inflammation caused by activated T-cells. Infiltration with T-cells is commonly seen in both the peripheral and central nervous systems in cases of anti-Hu antibody-associated PNS (9). Since the effect of IVIg is believed to involve interference with the passage of activated immune cells across the blood-nerve barrier (10), the present patient might show disappearance of the cauda equina enhancement after IVIg treatment. Unfortunately, the axonal degeneration may be too progressive to respond to IVIg therapy. To our best knowledge, the present case is the first in which cauda equina enhancement appeared in a patient with anti-Hu antibody-associated PNS.

Although the initial appearance of the brain lesions in this

case suggested brain metastasis of SCLC, the reversible nature of the disease made us reconsider the possibility of paraneoplastic encephalopathy. Anti-Hu antibody-associated PNS often results in CNS involvement, such as limbic encephalitis, although the cingulate cortex, a target in the present case, is rarely involved (11, 12). Rudzinski et al. reported the cerebral MRI findings in 28 patients with anti-Hu antibody-associated encephalitis. Among these patients, the lesions appeared in the temporal lobe in six patients, hippocampus in three patients and cingulate gyrus in two patients (13). In addition to the cingulate cortex, the present patient exhibited lesions in extralimbic areas, such as the prefrontal cortex. These findings clearly indicate that extralimbic involvement can also occur in patients with anti-Hu antibody-associated PNS. Although the serum titer of anti-Hu antibodies was not remarkably reduced after chemotherapy, anti-SCLC chemotherapy improved the encephalopathy

noted in the present case. While reversible brain lesions are an infrequent presentation of PNS, such lesions should be noted in order to distinguish PNS from direct brain metastasis.

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

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