CASE REPORT

Anti-Hu-associated Paraneoplastic Encephalomyelitis with Esophageal Small Cell Carcinoma

Toshihiko Shirafuji, Fumio Kanda, Kenji Sekiguchi, Masatsugu Higuchi, Hiroshi Yokozaki, Keiko Tanaka, Hitoshi Takahashi and Tatsushi Toda

Abstract

A 63-year-old woman had anti-Hu-associated paraneoplastic encephalomyelitis (anti-Hu syndrome) caused by esophageal small cell carcinoma (SCC). The patient developed bilateral limbic encephalitis, followed by myelitis, brain stem encephalitis, and autonomic failure. Extensive examination demonstrated SCC of the abdominal lymph nodes that was retrospectively diagnosed as metastasis of esophageal SCC on autopsy. The neuropathological findings were characterized by widespread neuronal loss and gliosis in the central nervous system, as well as patchy loss of myelin and axons in the spinal nerve roots with perivascular lymphocytic infiltration. This is the first detailed clinical and neuropathological report of anti-Hu syndrome caused by esophageal SCC.

Key words: anti-Hu-associated paraneoplastic encephalomyelitis, esophageal small cell carcinoma, multiple lesions


Introduction

Anti-Hu-associated paraneoplastic encephalomyelitis (anti-Hu syndrome) is the most frequent remote effect of cancer, potentially affecting the entire nervous system (1-3). Overall, 61-87% of anti-Hu syndrome cases were associated with pulmonary small cell carcinoma (SCC) (1-5). Only a few cases of anti-Hu syndrome associated with extra-pulmonary SCC have been reported. Anti-Hu syndrome related to SCC of the esophagus is extremely rare (2).

While a common clinical manifestation of the anti-Hu syndrome is sensory neuronopathy, 70% of patients have multiple clinical neurological symptoms and 34% of patients have 3 or more areas of involvement in the nervous system (3) during the course of the disease. There have been only a few reports which discuss multiple regional involvement in the nervous system (6, 7).

A case of anti-Hu syndrome with various paraneoplastic neurological syndromes, including, limbic encephalitis, subacute necrotizing myelitis, and brain stem encephalitis is presented. This is the first detailed clinical and neuropathological report of anti-Hu syndrome with esophageal SCC.

Case Report

A 63-year-old woman who complained of amnesia for one month was referred to our hospital for further examinations. On neurological examination, disorientation and emotional instability were evident. Cortical symptoms, such as aphasia or apraxia, were absent. The Mini-Mental State Examination (MMSE) score was 12/30. The total-intelligence quotient (IQ) was 73 (verbal IQ 79, performance IQ 68) on the Revised Wechsler Adult Intelligence Scale (WAIS-R).

Neurological examination revealed mild weakness of hip flexor bilaterally. Reflexes were increased in bilateral biceps and patellar tendons, and the right Achilles tendon, but were decreased in bilateral triceps and left Achilles tendons. Bilateral plantar responses were indifferent. There was no ataxia or sensory impairment.
Abdominal CT showed two, 2 to 3 cm diameter, round lymph nodes enhanced with gadolinium. A FLAIR image of the brain showed high signal intensities in the white matter and bilateral medial temporal lobes including the hippocampus and amygdala (Fig. 1). Laboratory tests revealed an increased concentration of serum pro-gastrin-releasing peptide (proGRP) at 69 pg/mL (<45 pg/mL), but serum neuron-specific enolase (NSE) was within normal limits. Cerebrospinal fluid contained 5 white blood cells/μL. Protein and IgG concentrations were 69 mg/dL and 9.4 mg/dL, respectively, and oligoclonal bands were positive in cerebrospinal fluid. Anti-Hu antibody was confirmed in the patient's serum, and oligoclonal bands were positive in cerebrospinal fluid. Nerve conduction studies revealed many fasciculation potentials with few fibrillation potentials and positive sharp waves (fib/PSW) before the biopsy. Many fib/PSW with a few fasciculation potentials in the right biceps brachii were observed during the progression of the muscular weakness. No waxing or waning phenomenon was observed with repetitive nerve stimulation.

Neither intravenous immunoglobulin infusion therapy (400 mg/kg daily for 5 days) at week 5 nor intravenous methyl-prednisolone pulse therapy (1,000 mg daily for 3 days) at week 10 showed any benefit for her condition.

At weeks 6 to 10, impairment of cranial nerves VI, VII, IX, and X developed and were followed by autonomic malfunctions including orthostatic hypotension, unstable pulse rate, and decreased bowel sounds. The patient developed a succession of bouts of pneumonia at weeks 21, 30, and 40. At week 21, her consciousness level deteriorated to a deep coma. There was flaccid paralysis of all extremities. All tendon reflexes were disappeared. Bilateral plantar responses were indifferent. There was no involuntary movement. The patient died of sepsis 10 months after the onset of the neurological symptoms.

**Autopsy findings**

A general autopsy was performed about 14 hours after death, at which time the brain weighed 1,280 g. The brain and spinal cord were fixed with 10% formalin, and multiple tissue blocks were embedded in paraffin. Histological examination was performed on 4-μm-thick sections using several stains, including hematoxylin and eosin, Klüver-Barrera, Bodian, and Holtzer. Immunohistochemical examination was also carried out: the spinal cord sections, with the anterior and posterior nerve roots, and esophageal cancer tissue sections were immunostained using an antibody against phosphorylated neurofilament (SMI-31, Sternberger Monoclonals, Bethesda, MD, USA).

**Macroscopic findings**

A general autopsy revealed a tumor arising in the middle part of the esophagus (Fig. 2) with metastasis to the regional para-aortic lymph nodes, which was later shown histopathologically to be SCC; the tumor cells were positive for cytokeratin, CD56 and synaptophysin (data not shown). There was no lymph node involvement other than the regional lymph nodes, consistent with the limited disease (LD).

The brain, including brain stem, cerebellum, and spinal cord, was almost entirely soft and pale. The cerebral cortex showed thinning and pale-brownish discoloration, being more marked in the lateral temporal lobe. The subcortical white matter also showed a coarse granular appearance.

**Microscopic findings**

Histopathological examination of the brain and spinal cord revealed apparent neuronal loss and gliosis in almost the entire cerebral cortex, brainstem lower motor neuron nuclei [severe in the oculomotor (III) and hypoglossal (XII)]...
Figure 2. A tumor in the middle region of the esophagus (A), consisting of small cancer cells (B) (Hematoxylin and Eosin staining).

Figure 3. Neuronal loss and gliosis in the lower motor neuron nuclei: severe in the oculomotor (III) (A) and hypoglossal (XII) (B) nuclei; moderate in the motor nuclei of the trigeminal (V) (C) and facial (VII) nerves (D); and mild in the nucleus ambiguus (E). In the hippocampus, CA1-2 and the subiculum (F) are relatively preserved. However, severe neuronal loss and gliosis are evident in CA3-4 (G). Moderate neuronal loss is observed in the putamen (H) and thalamus (I).

nuclei; moderate in the motor nuclei of the trigeminal (V) and facial (VII) nerves; and mild in the nucleus ambiguus, hippocampus (severe in CA3-4, relatively preserved in CA1-2 and the subiculum), parahippocampal gyrus (moderate), amygdala (severe in the medial part), caudate nucleus (moderate), putamen (moderate), thalamus (moderate), brainstem reticular formation including the raphe nucleus (severe), gracile and cuneate nuclei (severe), inferior olivary nucleus (severe), and spinal gray matter (severe in the anterior horn, relatively preserved in the posterior horn and intermedio-lateral nucleus) (Fig. 3, Fig. 4B, and Table). There was diffuse myelin pallor in the cerebral white matter. Diffuse myelin pallor with macrophage infiltration was also evident in the brainstem (central tegmental tract and medial leminiscus) and spinal cord (Fig. 4A). There was patchy myelin pallor in both spinal anterior and posterior nerve roots (Fig. 4C).
Table. Degree of Neuronal Loss in the Central Nervous System

<table>
<thead>
<tr>
<th>Degree of neuronal loss</th>
<th>Site</th>
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<tr>
<td>Severe</td>
<td>oculomotor nuclei, hypoglossal nuclei, hippocampus (CA3-4), amygdala, raphe nucleus, gracile and cuneate nuclei, inferior olivary nucleus, anterior horn, Purkinje cell</td>
</tr>
<tr>
<td>Moderate</td>
<td>nuclei of the trigeminal and facial nerve, hippocampus (CA1-2 and subiculum), parahippocampal gyrus, caudate nucleus, putamen, thalamus, posterior horn and intermediolateral nucleus, cerebellar dentate nucleus</td>
</tr>
<tr>
<td>Mild</td>
<td>nucleus ambiguus</td>
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Immunostaining with SMI31, a marker for axon, also showed patchy axonal damage (Fig. 4D). Purkinje cell loss and Bergmann’s gliosis were evident in the cortex, being more marked in the superior part of the vermis. The cerebellar dentate nucleus was relatively well preserved. Occasional perivascular and intraparenchymal lymphocytic infiltration was seen throughout the entire affected regions. A few microglial nodule- and neuronophagia-like lesions were also seen in the affected brainstem and spinal gray matter.

Discussion

The present case was characteristic in its combination of symptoms of mental deterioration, upper and lower motor neuron disturbance, and various autonomic system failures with rapid progression. Extensive work-up for the origin of the malignancy was negative, and an autopsy first revealed the esophageal SCC. We concluded that the neurological deficit was caused by a paraneoplastic etiology because there was no tumor invasion in the nervous system. Moreover, since anti-Hu antibody was detected in her serum, this patient was diagnosed with anti-Hu syndrome.

The autopsy examination showed severe disintegration in the major part of the brain in the present patient. It was difficult to determine whether the damage originated from the hypoxia due to the pneumonia or the anti-Hu syndrome. Despite the softness of the brain, global ischemia or hypoxia could be excluded because the vulnerable regions for hypoxia including the basal ganglia, Ammon’s horn, tegmentum, substantia nigra, and calcareum, were relatively preserved microscopically. Moreover, whole layer involvement, not laminar necrosis, was evident throughout the entire cortex. These findings suggested that the broad damage of the
nervous system was due not to hypoxia but to the anti-Hu syndrome.

The characteristic pathological findings of anti-Hu syndrome with pulmonary SCC are neuronal loss with reactive gliosis, microglial proliferation, and perivascular lymphocytic cuffing (9). In the present case, neuronal loss with gliosis and lymphocytic infiltration in the brain including brain stem, cerebellum, and spinal cord was confirmed. It was indicated that neuropathological features in anti-Hu paraneoplastic neurological syndromes caused by esophageal SCC were similar to those by pulmonary SCC.

During the course of the anti-Hu syndrome, multiple areas of the nervous system became involved in 70% of the patients (2, 3). However, only a limited number of neuropathological studies of anti-Hu syndrome with multiple areas involvement has been reported (6, 7). Multiple neuropathological lesions correlated with the multiple clinical symptoms were confirmed in the present case. Neurological complications, mostly ventilatory failure and dysautonomia, appear to be the most common causes of death (3), as in the present case.

Because the symptoms of anti-Hu syndrome tend to occur before tumor detection, it is important to know the candidate organs for the primary site. Esophageal SCC is one of the common sites of extrapulmonary SCC (10). However, there have been reports of a few paraneoplastic syndrome cases with esophageal carcinoma (11-15). Moreover, anti-Hu syndrome with esophageal carcinoma was reported in only 1 of 200 patients without pathological study (2). Therefore, to the best of our knowledge, this is the first detailed report of anti-Hu syndrome related to esophageal SCC. The present case showed that esophageal SCC could be a cause of the anti-Hu syndrome. It is necessary to consider esophageal SCC as a candidate primary lesion responsible for anti-Hu syndrome.

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

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References


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