Anti-Hu associated paraneoplastic sensory neuronopathy with upper motor neurone involvement

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Paraneoplastic neurological syndrome is characterised by neuronal degeneration with lymphocytic infiltration in various regions of the central and peripheral nervous systems. Motor neurone symptoms may occur as a remote effect of malignancy, and have been considered because of the involvement of lower motor neurones. A case is reported of an 80 year old woman suffering from paraneoplastic sensory neuronopathy with anti-Hu antibody. Postmortem examination showed adenocarcinoma of the gall bladder and small cell carcinoma of the duodenum. Neuronal loss with lymphocytic infiltration was found in the dorsal root ganglia, brain stem, and cerebellum. Despite the absence of upper motor neurone signs, there was severe loss of Betz cells and degeneration of the bilateral pyramidal tracts. To our knowledge, this is the first demonstration of upper motor neurone involvement in anti-Hu associated paraneoplastic syndrome.

Paraneoplastic encephalomyelitis and sensory neuronopathy (PEM/PSN) with anti-Hu antibody is pathologically characterised by neuronal depletion with lymphocytic infiltration in various regions of the central and peripheral nervous systems, including the limbic system, brain stem, cerebellum, spinal cord, and dorsal root ganglia. Paraneoplastic processes may also affect the upper and lower motor neurones. Loss of anterior horn cells in the spinal cord and neurons in patients with anti-Hu associated motor neurone syndrome. Subacute motor neuroneopathy found in patients with Hodgkin’s disease and other lymphoproliferative disorders has been described as a pure lower motor neurone syndrome. Subacute motor neurone involvement of lower motor neurones. A case is reported of an 80 year old woman suffering from paraneoplastic sensory neuronopathy;

Methods
The cerebral hemispheres were sectioned coronally and samples were taken from multiple cortical areas, including the basal ganglia, thalamus, midbrain, pons, medulla oblongata, cerebellum, spinal cord, and dorsal root ganglia. The tissue blocks were embedded in paraffin wax, sectioned at a thickness of 4 μm, and stained with either haematoxylin and eosin or by the Kluver-Barrera method. Other sections were immunostained using monoclonal antibodies against ubiquitin (Dako, Glostrup, PAS, and immunostaining for oligoclonal bands were performed. Sural nerve biopsy showed severe loss of large myelinated fibres (fig 1A). Laboratory tests showed increased concentrations of neurone specific enolase (90.9 ng/ml), progastrin releasing peptide (829 pg/ml), carcinoembryonic antigen (8.3 ng/ml), and CA19–9 (86.5 U/ml). Moreover, protein concentration (0.73 g/l). Although abdominal CT was performed again, it showed findings similar to those obtained previously. Gastrofibrescopy showed a submucosal tumour covered by intact mucosa in the posterior wall of the duodenal bulb. Therefore, we suspected that the underlying malignancy was carcinoma of the gall bladder with metastasis to the abdominal lymph nodes. The patient eventually developed muscle weakness and died of pulmonary failure eight months after onset of the neurological symptoms. No upper motor neurone signs were noted during the course of the illness.

CASE REPORT
Clinical course
An 80 year old woman developed paresthesia with a glove and stocking distribution in June 2001. She consulted a physician on 9 October 2001, because of left facial nerve palsy, anorexia, and severe weight loss. She gradually became unable to stand up because of progressive sensory ataxia despite only mild muscle weakness of her legs. Computed tomography (CT) of the brain and chest showed no abnormalities. An abdominal CT scan demonstrated thickening of the gall bladder wall and a mass lesion situated dorsal to the duodenum. She was suspected of having paraneoplastic neurological disease, and was admitted to our hospital on 15 November 2001. On neurological examination, her mental status was normal, but she appeared distressed because of severe pain and paresthesia. Her left facial nerve palsy had already improved. She showed severe deficits of all sensory modalities in her hands and feet and was unable to roll over in bed. There was diffuse muscle wasting, but no fasciculation was evident. There was no apparent cerebellar ataxia or pseudoneosthenosis in her hands. Left triceps and bilateral ankle jerks were absent, and Babinski’s signs were negative. Sensory nerve action potentials of the median and sural nerves could not be elicited. Motor nerve conduction velocities were slightly decreased (ulnar nerve, 42.9 m/s; tibial nerve, 37.8 m/s). Needle electromyography was not performed. Sural nerve biopsy showed severe loss of large myelinated fibres (fig 1A). Laboratory tests showed increased concentrations of neurone specific enolase (90.9 ng/ml), progastrin releasing peptide (829 pg/ml), carcinoembryonic antigen (8.3 ng/ml), and CA19–9 (86.5 U/ml). Moreover, presence of anti-Hu antibody was confirmed in her serum (the titre was >2000). No oligoclonal bands were found in the cerebrospinal fluid. Examination of the cerebrospinal fluid showed mild pleocytosis (19/3 cells) and an increased protein concentration (0.73 g/l). Although abdominal CT was performed again, it showed findings similar to those obtained previously. Gastrofibrescopy showed a submucosal tumour covered by intact mucosa in the posterior wall of the duodenal bulb. Therefore, we suspected that the underlying malignancy was carcinoma of the gall bladder with metastasis to the abdominal lymph nodes. The patient eventually developed muscle weakness and died of pulmonary failure eight months after onset of the neurological symptoms. No upper motor neurone signs were noted during the course of the illness.

Abbreviations: CT, computed tomography; PEM/PSN, paraneoplastic encephalomyelitis and sensory neuronopathy; ALS, amyotrophic lateral sclerosis

Necropsy findings

General necropsy showed adenocarcinoma of the gall bladder and small cell carcinoma of the duodenum. No metastatic foci were found anywhere. The brain weighed 1055 g and was slightly atrophic. Histopathological examination showed loss of neurones with mild lymphocytic infiltration in the dorsal root ganglia and degeneration with many macrophages in the posterior column of the spinal cord. Severe loss of Purkinje cells with Bergmann’s gliosis (fig 1C) and mild loss of granule cells were found in the cerebellar cortex. In the brain stem, there were scattered perivascular lymphocytic cuffsing and occasional neuromophagia (fig 1C). Moreover, severe loss of Betz cells was observed in the motor cortex (fig 1D), and gliosis was evident in the deeper cortical layers and the convolutional white matter (fig 1E). In the spinal cord, degeneration with many macrophages was found in the bilateral pyramidal tracts (fig 1F); myelin pallor was evident up to the medullary pyramids and macrophages were noted in the corticospinal tracts up to the cerebral peduncle. There was mild to moderate loss of anterior horn cells. No Bunina bodies or ubiquitin positive skein-like inclusions, which are characteristic of amyotrophic lateral sclerosis (ALS), were found in the remaining anterior horn cells or brain stem motor neurones.

DISCUSSION

Our patient was clinically diagnosed as having PSN with anti-Hu antibody. Postmortem examination showed that our patient had two carcinomas, one of which was adenocarcinoma of the gall bladder and the other small cell carcinoma of the duodenum. Although the duodenum is a rare site for occurrence of small cell carcinoma, the most common underlying tumour of anti-Hu-associated PEM/PSN is small cell carcinoma.2,4 Graus et al have reported that small cell carcinoma was found in 114 of 149 patients (77%); 111 of the tumours were located in the lung, and 3 of the 114 patients had another tumour (lung adenocarcinoma in two and breast cancer in one) coexisting with small cell lung carcinoma.2 The neuropathological findings in our patient were consistent with those of PEM/PSN; neuronal loss with inflammatory changes was observed in the cerebellum, brain stem, spinal cord, and dorsal root ganglia.7 Furthermore, severe loss of Betz cells and degeneration of the bilateral pyramidal tracts were evident. These last findings have not been described previously in PEM/PSN. Focal lesions causing secondary degeneration of the pyramidal tracts, such as infarcts or haemorrhages, were not noted in the cerebrum and brain stem in our patient. In addition, Betz cells in the motor cortex were considerably depleted bilaterally. Coincidental occurrence of ALS was unlikely, because Bunina bodies and skein-like inclusions, which are consistent neuronal inclusions in ALS, were not found in the lower motor neurones. Therefore, we considered that the upper motor neurone involvement in this patient was also a paraneoplastic complication.

Previously, several investigators have described motor neurone syndrome as a remote effect of cancer.1,2,7–12 Dalmau et al reported that motor neurone dysfunction was a predominant symptom in 14 of 71 patients (20%) with anti-Hu associated PEM/PSN, and that none of the patients developed pure motor neurone syndrome mimicking ALS.7 However, there have been only a few necropsy studies of paraneoplastic motor neurone syndrome. Brain et al described the clinical features of 11 patients with paraneoplastic motor neurone disease. Two of them had a necropsy, and both showed loss of anterior horn cells; furthermore, myelin pallor was observed in the bilateral pyramidal tracts up to the medullary pyramids in one of them.7 Verma et al reported a necropsy case of motor neurone disease associated with small cell lung carcinoma and anti-Hu antibody, in which postmortem examination showed loss of anterior horn cells in the spinal cord but normal corticospinal tracts.7 Forsyth et al described three cases of rapidly progressive motor neurone syndrome with anti-Hu antibody.2 Postmortem examinations were performed in two of the three patients, and both showed striking depletion of the anterior horn cells in the spinal cord but no abnormalities in the corticospinal tracts. Moreover, there have been several clinical reports of female patients with upper motor neurone syndrome (primary lateral sclerosis) associated with breast cancer.2,13 A case of anti-Yo associated motor neurone syndrome with
signs of upper motor neurone disorder has also been reported.11 Loss of neurones in the motor cortex with bilateral degeneration of corticospinal tracts has been reported in some patients with lymphoproliferative disorders.5 Recently, Berghs et al described autoantibodies directed against axon initial segments and nodes of Ranvier of myelinated fibres, including the axons of motoneurones, in a patient with paraneoplastic lower motor neurone syndrome and breast cancer.13 Paraneoplastic motor neurone disease may result from autoimmunity directed against antigens shared by the affected neurones and the associated cancer cells. In conclusion, both the upper and lower motor neurones may be involved in the disease process of paraneoplastic neurological syndrome with or without anti-Hu antibody.

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