

SHORT REPORT

Spontaneous neurological improvement in anti-Hu associated encephalomyelitis

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Abstract

Symptoms of anti-Hu associated paraneoplastic encephalomyelitis (PEM) and sensory neuropathy (PSN) are usually severe and irreversible. Two patients are reported whose symptoms improved spontaneously, and in one of them they resolved after resection of an inflammatory lesion of the lung. Spontaneous neurological improvement, although rare, should be considered in the evaluation of therapies for PEM/PSN.

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Most patients with anti-Hu associated paraneoplastic encephalomyelitis (PEM) and sensory neuropathy (PSN) have severe neurological disability, and symptoms do not respond either to immunosuppressive agents or to successful treatment of the tumour, usually a small cell lung cancer.¹⁻³ Although some patients with high titre anti-Hu antibodies may develop indolent neuropathies,⁴ spontaneous improvement of anti-Hu associated PEM/PSN has never been reported. We describe two patients with anti-Hu associated PEM/PSN whose neurological symptoms improved or resolved without cancer therapy or immune suppressants.

Case report 1

In October, 1992 a 67 year old woman with a 100 pack-year smoking history developed cough and weight loss. She had complained of progressive bilateral leg pain for the past year. A chest CT demonstrated two right upper lobe lung nodules (12 × 13 mm and 13 × 18 mm), right upper lobe peribronchial thickening consistent with lymphatic obstruction, and extensive mediastinal and right hilar adenopathy. A tuberculin test was negative. In November 1992, mediastinoscopic biopsy of several lymph nodes disclosed lymphohyperplasia, histiocytic hyperplasia, fibrosis, and anthracosis, but no malignancy. Bronchial washings were negative and no treatment was instituted. By December 1992, the chest CT showed

improvement of the parenchymal, hilar, and mediastinal abnormalities. In January 1993, the patient developed diplopia with dysconjugate gaze. Acetylcholine receptor antibodies, Lyme serology, and thyroid function tests were normal. In March 1993, a neurological consultant reported progressive gait unsteadiness, paraesthesiae, burning shin and hand pain, and persistent diplopia. The patient reported a 20 pound weight loss over the previous few months and general weakness. Neurological examination showed a chronically ill looking woman with vertical nystagmus, dysconjugate gaze, dysarthria, gait ataxia, and hyperaesthesia and dysaesthesia to light touch over her limbs. Strength, tendon reflexes, and heel-to-shin and finger-to-nose tests were normal. Head MRI showed small bilateral frontal subcortical areas of increased signal on T2 images, without abnormal contrast enhancement, consistent with mild ischaemic changes. Blood studies including complete blood count, liver function tests, CA-125, creatine kinase, serum protein electrophoresis, B12, folic acid, FTA-ABS titres, and repeated Lyme serology were normal; serum anti-Hu antibodies (examined by immunohistochemistry of human cerebral cortex and immunoblots of isolated human neurons and recombinant HuD, as previously reported)^{5,6} were positive at high titre (1:64 000). Cerebrospinal fluid had a normal opening pressure, three mononuclear cells, 0 red blood cells, 47 mg/dl protein (normal 15-45), 53 mg/dl glucose (normal 40-70), oligoclonal bands not present in serum, positive anti-Hu antibodies (1:32,000), negative venereal disease research laboratory test and Lyme serologies, negative cytology, and negative cultures for bacteria and fungus. Sensory action potentials were absent in the ulnar and sural nerves and prolonged in the median nerve.

A repeat chest CT performed in April 1993 demonstrated a decrease in the size of the two right upper lung nodules and resolution of the mediastinal and hilar adenopathy. Given the suspicion that the patient was harbouring a primary carcinoma of the lung, she underwent a right upper lobectomy in May 1993; pathological examination disclosed infiltrates of lymphocytes, plasma cells, and fibrosis, but no cancer. Sections of a lesion incubated with

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biotinylated anti-Hu IgG showed no reactivity, indicating absence of microscopic small cell lung cancer.

During the month before the lung surgery the patient considered that her neurological symptoms were improving, without taking any medication; however, a much more rapid improvement occurred after lobectomy. By the end of May, neurological examination showed vertical nystagmus, without dysconjugate gaze, and improvement of the gait ataxia and leg pain. By August, she was able to return to full time employment as a machinist, experiencing only one brief episode of gait disturbance and blurred vision. In September, a chest CT was normal. Periodic neurological examinations during March 1994 were remarkable only for trace vertical nystagmus, and by January 1996 the neurological examination was entirely normal. The titre of anti-Hu antibodies had decreased to 1:500.

Case report 2

In summer 1995 a 62 year old woman with a 35 pack-year history of cigarette smoking developed pathological hypersomnia necessitating a reduction in her working hours by about 60%. Shortly thereafter she developed difficulty with vertical eye movements which interfered with walking and descending stairs, myoclonic tremors of the arms, and episodes of severe weakness associated with amnesia, disorientation, and hallucinations. In September, investigations for subacute dementia including vitamin B12 and folate, electrolyte, liver and renal profiles, endocrine investigations, brain MRI, and investigation for malignancy including chest radiograph and tumour markers (carcinoembryonic antigen and β_2 -microglobulin) were unremarkable. Three lumbar punctures showed from 9–20 mononuclear cells, 300–400 red blood cells/mm³, a raised protein concentration (80 mg/dl), normal glucose, negative cytology, cultures, Lyme and venereal disease research laboratory test serologies, and negative tumour markers.

Symptoms progressed rapidly with increasing hypersomnolence and myoclonus, alternating with periods of alertness without orientation or insight. In October she was admitted to hospital where neurological examination was remarkable for a fluctuating level of consciousness, poorly reactive asymmetric pupils, vertical supranuclear gaze palsy, and upper extremity myoclonus and ataxia. Sensory examination and tendon reflexes were normal. Serial EEGs demonstrated bilateral diffuse slowing, but no paroxysmal epileptiform activity. The patient became stuporous, and received ceftriaxone for two weeks for a presumptive diagnosis of Whipple's disease (final PCR analysis of CSF negative), together with 60 mg/day prednisone and 40 mg/day dexamethasone, for four days each, to prevent a possible Jarisch-Herxheimer reaction. There was no response to this treatment and further deterioration prompted an open biopsy of the right temporal lobe, which disclosed scattered

mild subpial gliosis and a minimal perivascular mononuclear infiltrate of leptomeningeal small vessels. A search for neoplasia disclosed high titre anti-Hu antibodies in serum (1:64 000) and CSF (1:16,000). CT of the thorax showed bilateral mediastinal adenopathy. Biopsy of a left supraclavicular lymph node showed small cell lung cancer. She was considered too neurologically devastated to receive chemotherapy, and no specific treatment was offered for the paraneoplastic disorder. However, by November she had improved sufficiently to be discharged home where over the subsequent two months she continued to improve with attenuation of myoclonic tremor, normalisation of the sleep-wake cycle, and disappearance of the episodes of weakness, disorientation, and hallucinations. In February 1996, she developed severe pruritus unresponsive to antihistamine drugs and a brief trial of prednisone. CT disclosed slight progression of mediastinal adenopathy, but no new lesions. In April she was fully oriented and alert and could engage in normal conversation, but had mild difficulty with recent memory. She complained only of severe unrelenting thoracic pruritus. The supranuclear gaze palsy persisted, but myoclonus was reduced to a mild tremor of outstretched arms. CT showed new hepatic metastases. Given her remarkable neurological improvement, she began treatment with cyclophosphamide, etoposide, and prednisone. The tumour and neurological symptoms remained stable during six cycles of chemotherapy. The pruritus was greatly improved on a low dose of methadone (4 mg every six hours). Recently, the patient developed anorexia and fatigue, and CT studies demonstrated tumour progression in the chest and liver. There were no new neurological deficits, and chemotherapy with adriamycin and vincristine has been started. The serum titres of anti-Hu antibodies have decreased to 1:16 000.

Discussion

These patients are presented to emphasise that, although rare, spontaneous neurological improvement sometimes occurs in patients with anti-Hu associated PEM/PSN.

In the absence of a positive biopsy, it could be questioned whether the first patient had lung cancer. We think that she did because anti-Hu antibodies have never been reported in normal subjects or in patients with systemic or autoimmune disorders.^{7,8} High titres of anti-Hu antibodies are always associated with PEM/PSN; low titres of anti-Hu antibodies are found in 16% and 4% of neurologically normal patients with small cell lung cancer and neuroblastoma respectively.^{5,9} Thus we think that even in the absence of histological proof, it is likely that the first patient had a spontaneously regressing small cell lung cancer in association with the paraneoplastic syndrome. Although highly unusual, spontaneous resolution of small cell lung cancer has been reported in patients with paraneoplastic syndromes.^{10,11} In addition, the tumours of

patients who harbour anti-Hu antibodies, either at high or low titre, seem to behave more indolently than the tumours from patients without anti-Hu antibodies.^{1 5 9 12}

Spontaneous improvement of anti-Hu associated PEM/PSN has not been reported. In our first patient, the neurological improvement started before any treatment and may have been enhanced by resection of a presumed lung cancer. This patient eventually had total resolution of symptoms without any further treatments.

The second patient received steroids to prevent a possible Jarisch-Herxheimer reaction; this treatment, given over an eight day period, did not affect the neurological disorder, which continued to progress. The neurological improvement started spontaneously several weeks later, and continued for several months, at which time the small cell lung cancer was found to have metastasised to the liver. This shows that spontaneous improvement of anti-Hu associated PEM does not require treatment or regression of the associated small cell lung cancer.

Given the severe neuropathology of anti-Hu associated PEM/PSN, and the generally rapid development of neurological symptomatology,^{1 13} it is surprising that significant remissions, whether spontaneous or treatment induced, can occur. In these patients, it is likely that inflammation and the immune response damaged but did not kill neurons. Pathological findings in another of our patients with anti-Hu associated limbic encephalitis who retained hippocampal neurons despite severe inflammation and gliosis supports this hypothesis.¹³ In disorders in which the neuronal cell body remains intact, such as in Lambert-Eaton myasthenic syndrome and perhaps opsoclonus/myoclonus, recovery might be expected if the underlying disorder is treated or, as sometimes occurs in limbic encephalitis and opsoclonus/myoclonus, symptoms may improve spontaneously.¹⁴ The disorders that have the greatest likelihood of experiencing spontaneous regression are those that have often been reported to respond to treatment.^{14 15} Because most large series¹⁻³ show that anti-Hu or anti-Yo associ-

ated paraneoplastic syndromes do not respond to treatment, isolated case reports should be viewed with caution.^{2 16} Our two patients indicate that spontaneous improvement of anti-Hu associated PEM/PSN can occur; this possibility should be considered whenever the response to new therapies is evaluated.

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