A 50-Year-Old Woman With Bilateral Vocal Cord Paralysis and Hilar Mass

Tereza Martinu, MD; and Alison S. Clay, MD

(CHEST 2005; 128:1028–1031)

A 50-year-old, white woman presented with a 5-month history of failure to thrive and hoarseness. The patient described a progressive decline in her voice, resulting in inability to speak. Concurrently, dysphagia, nausea, and alternating episodes of diarrhea and constipation developed, which resulted in the loss of 35 lb. Vertigo and dizziness became so severe that the patient was eventually unable to stand without falling. She also described headaches, anxiety attacks, an inability to move her eyes, and loss of visual acuity. The patient presented to an outside hospital where otolaryngologic evaluation revealed bilateral vocal cord paralysis. The patient underwent tracheostomy, and a gastrostomy tube was placed for severe weight loss. The patient was transferred to our institution for further evaluation.

During the 4 years prior to her hospitalization, the patient had been seen for multiple somatic and psychiatric complaints, including paresthesias, intermittent vertigo, anxiety, and depression. Based on serologic markers and the presence of mediastinal adenopathy on chest radiography, the patient received a diagnosis of sarcoidosis and/or lupus.

The patient’s other medical history was significant for congestive heart failure, hypertension, and gastroesophageal reflux disease. The patient had a 100-pack-year history of tobacco use. She had no occupational exposures or pets. The patient’s family history was remarkable for a mother with breast cancer and a grandfather with colon cancer.

On physical examination, the patient’s supine BP was 114/74 mm Hg with a pulse of 74 beats/min. Her upright BP was 90/62 mm Hg, with a pulse rate of 85 beats/min. Her temperature was 37.2°C, respiratory rate was 16 breaths/min, and oxygen saturation was 92% on 1 L of oxygen. Generally, the patient appeared cachectic, chronically ill, and older than her stated age. The pupils were accommodating but nearly unreactive to light. There were three to four beats of vertical nystagmus. The patient had marked temporal wasting and tongue fasciculations. There were no oral lesions or cervical, occipital, or suprACLavicular lymphadenopathy. A tracheostomy was in place. The lung fields had poor air exchange, and occasional wheezes were heard. The heart examination revealed regular rate and rhythm without murmurs, rubs, or gallops. The abdomen was remarkable for the presence of a gastrostomy tube and was diffusely tender and slightly distended without hepatomegaly. Neurologic examination was remarkable for global proximal muscle weakness (4/5) and pathologically brisk patellar, biceps, and brachioradialis reflexes. The patient had mild dysmetria. She had normal tone, normal sensation to pin prick, and down-going toes bilaterally.

Laboratory examination revealed a hemoglobin of 9.9 g/dL (normal range, 12.0 to 15.5 g/dL), mean cell volume of 100 femtoliters (normal, 80 to 98 femtoliters), WBC count of 15.7 × 10^3/μL (3.2 to 9.8 × 10^3/μL), and a platelet count of 552 × 10^3/μL (normal range, 150 to 450 × 10^3/μL). Chemistries, electrolytes, and coagulation profiles were all within normal limits. Thyroid-stimulating hormone was 0.21 μIU/mL (normal, 0.34 to 5.66 μIU/mL), and free thyroxine level was 0.57 ng/dL (normal, 0.52 to 1.21 ng/dL). Serum rapid plasma reagin was nonreactive. The erythrocyte sedimentation rate was 22 mm/h (normal, 0 to 15 mm/h), the anti-nuclear antibody titer was positive at 1:2560 dilution (high titer) with speckled and nucleolar patterns, and the anti-DNA antibody was 9 IU/mL (negative defined as < 30 IU/mL). An HIV-1 antibody test result was negative. Analysis of cerebrospinal fluid was completely normal.

A CT of the chest revealed a 2- by 2.3-cm left hilar mass and a small area of honeycombing (Fig 1). MRI of the brain showed nonspecific foci of T2 hyperintensity within the periventricular white matter, predominantly within the right cerebral hemisphere. Electromyography demonstrated typical myopathic motor units at the right deltoid without signs of acute or chronic denervation. Direct laryngoscopy revealed true bilateral vocal cord paralysis. The cords...
were fixed in the paramedian position with bilateral bowing of the cords and decreased laryngeal elevation (Fig 2).

What additional tests are needed at this point in order to establish the diagnosis?
Discussion

Paraneoplastic syndromes occur in 10 to 20% of patients with lung cancer. The most common paraneoplastic syndrome in lung cancer is hypercalcemia, seen most commonly in tumors of squamous cell histology. Of all the histologic forms of lung cancer, small cell lung cancer is associated with the greatest frequency and diversity of paraneoplastic syndromes, including paraneoplastic encephalomyelitis and sensory neuropathy, paraneoplastic cerebellar degeneration, cancer-associated retinopathy, opsoclonus-myoclonus, and Lambert-Eaton myasthenic syndrome. Nearly all these paraneoplastic syndromes are associated with the presence of atypical antibodies in the sera. Anti-Hu antibodies are associated with paraneoplastic encephalomyelitis, sensory neuropathy, cerebellar degeneration, and autonomic neuropathy.

Anti-Hu antibodies are anti-neuronal nuclear autoantibodies generated against the Hu antigen found in neurons. Because the developing CNS is sequestered from the immune system by the blood brain barrier, normal adults do not have Anti-Hu antibodies. However, anti-Hu antibodies may be produced in response to small cell lung cancer derived from neural crest cells. Although all small cell lung cancers express Hu antigen, < 20% of all patients with small cell lung cancer have detectable levels of anti-Hu antibodies. Sixty-seven percent of patients with anti-Hu antibodies have other systemic autoantibodies, including anti-nuclear antibody, and thus seem to have a genetic susceptibility to autoimmunity. Although anti-Hu antibodies have been found in ovarian, breast, prostate, and colon cancer, the presence of anti-Hu antibodies is almost always indicative of an underlying small cell lung cancer; the sensitivity and specificity of anti-Hu antibodies for the diagnosis of small cell lung cancer have been found to be 80 to 90%, respectively.

Patients with anti-Hu antibodies do not typically present with symptoms of occult lung cancer; usually they are first affected by neurologic symptoms related to antibody crossreactivity with central and peripheral nerves. Sensory polyneuropathy is the most common neurologic complaint. Other neurologic manifestations include motor and mixed somatic neuropathy, cerebellar symptoms, limbic encephalitis, cranial neuropathy, myopathy, movement disorder, and aphasia. Fasciculations may be present in patients with myopathy. Limbic encephalopathy manifests as seizures, confusion, dementia, depression, anxiety, or cognitive decline. Cerbellar symptoms include gait ataxia, action tremor, and scanning dysarthria. Brainstem involvement presents as oculomotor paresis, sensorineural hearing loss, and tongue fasciculations. Autonomic neuropathy with severe orthostatic hypotension often occurs. Nonneurologic symptoms have also been described. GI dysmotility occurs in > 20% of patients and is the initial complaint in 12% of patients with anti-Hu antibodies.

To our knowledge, true bilateral vocal cord paralysis has not been described in association with a paraneoplastic process. Bilateral vocal cord paralysis is a very rare diagnosis. The most common cause of bilateral vocal cord paralysis in adults is recurrent laryngeal nerve injury as a complication of thyroidectomy. In a review of 240 cases of adult bilateral abductor vocal cord paralysis, the following were found to be the cause of bilateral vocal cord paralysis: 55% of cases occurred following thyroidectomy, 22% had neurologic causes, 6% had malignancy of the neck, 14% had other causes, and 3% of adults were thought to have idiopathic vocal cord paralysis. In addition to this review, > 300 case reports of bilateral vocal cord paralysis have been written. In addition to trauma (blunt, surgical, or postintubation), medical causes of adult-onset bilateral vocal cord paralysis described in the literature include the following: myasthenia gravis; Guillain-Barre syndrome; postinfectious complications of herpes simplex virus, poliomylitis, diptheria, and Streptococcus pneumoniae meningitis; thyroiditis; hypokalemia; radiation-induced damage; cisplatin toxicity; vincristine toxicity; organophosphate poisoning; Shy-Drager syndrome; Parkinson disease; diabetes melitus; systemic lupus erythematosus; polyarteritis nodosa; and stroke. Vocal cord paralysis has also been described in the setting of disruption of both recurrent laryngeal nerves secondary to neck malignancies, and rarely in association with lung cancer.

Patients who present with anti-Hu paraneoplastic disease have a unique clinical course. Their cancer is usually limited to the mediastinum at the time of diagnosis and typically responds better to therapy. In one study of 196 patients with small cell lung cancer treated with standard chemotherapy, 55.6% of patients with anti-Hu antibodies had complete response to therapy, compared to 19.6% without anti-Hu antibodies. Spontaneous regression of small cell lung cancer has also been described. Some have postulated that anti-Hu antibodies are a marker for host defense against small cell lung cancer, thus explaining the limited size and location of this cancer at the time of diagnosis and better response to chemotherapy. Patients with anti-Hu antibodies usually do not die from their small cell lung cancer, but
rather from their neurologic disease. Patients often die from autonomic or respiratory complications of their PSN. Although patients have survived for many years with this disease, the median time to death is approximately 7 months. Unfortunately, treatment of small cell lung cancer does not reverse polysensory neuronopathy. Immunotherapy with plasmapheresis and high-dose steroids has been attempted to improve neurologic dysfunction with mixed results. Two series have shown that immunotherapy may prevent further neurologic decline, but this treatment does not reverse pretreatment neurologic dysfunction.

The diagnosis in our patient was made with anti-Hu paraneoplastic sensory neuronopathy based on a positive anti-neuronal nuclear antibody type-1 titer at 1:7,680 (negative is defined as < 1:60) and a transbronchial needle biopsy of the left hilar mass revealing small cell lung cancer (Fig 3). The bilateral vocal cord paralysis was thought to be a manifestation of the paraneoplastic process. The patient was treated with carboplatin and etoposide, as well as chest radiation therapy and prophylactic cranial radiation therapy. One and a half years after her initial presentation, she is alive, able to speak, and walks with a walker. As is the case with most patients with Anti-Hu paraneoplastic process, our patient continues to have neurologic problems including severe vertigo and seizures.

**Clinical Pearls**

1. Bilateral true vocal cord paralysis may be a manifestation of a paraneoplastic syndrome.
2. Small cell lung cancer associated with anti-Hu antibodies is usually localized to the mediastinum at time of diagnosis and has a less aggressive course than small cell lung cancer without anti-Hu antibodies.
4. Patients with small cell lung cancer and anti-Hu antibodies often die of complications of neurologic disease and not of cancer per se.

**Suggested Readings**


Lucchinetti CF, Kimmel DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. Neurology 1998; 50:653–657


**Figure 3.** Photomicrographs of transbronchial biopsy of left hilar mass. Left, A: Streak artifact characteristic of small cell cancer (hematoxylin-eosin, original × 20). Right, B: Small cell lung cancer cells demonstrating nuclear molding, scant cytoplasm, fine granular chromaffin, and inconspicuous nucleoli (solid arrow). Normal columnar respiratory ciliated cells can also be seen (dashed arrow). [Papanicolaou stain, original × 60].

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CHEST / 128 / 2 / AUGUST, 2005 1031

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