Small cell lung cancer with positive anti-Hu antibodies presenting as gastroparesis

David N Moskovitz MD BSc, Kenneth V Robb MD FRCPC

DN Moskovitz, KV Robb. Small cell lung cancer with positive anti-Hu antibodies presenting as gastroparesis. Can J Gastroenterol 2002;16(3):171-174.

Lung cancer is the most common cancer in North America. Small cell lung cancer (SCLC) represents 15% to 25% of lung cancers. SCLC commonly relapses, resulting in a 3% to 8% five-year survival rate. The poor prognosis associated with SCLC is partly due to late diagnosis of the disease. Paraneoplastic syndromes can be early manifestations of SCLC. The potential benefit of early diagnosis has prompted investigations into markers of this disease. Some patients may present with predominantly gastrointestinal dysmotility symptoms that have no obvious explanation. Testing for anti-Hu antibodies, as a valuable marker of SCLC, should be considered in the investigation. A case of SCLC with positive anti-Hu antibodies presenting with intestinal pseudo-obstruction is presented. Gastrointestinal dysmotility as a manifestation of paraneoplastic syndrome is reviewed.

Key Words: *Antinuclear antibodies; Hypomotility; Paraneoplastic syndrome; Small cell lung cancer*

Cancer du poumon à petites cellules, accompagné d'anticorps anti-Hu se présentant sous forme de gastroparésie

RÉSUMÉ : Le cancer du poumon, dont 15 à 25 % des cas sont des cancers du poumon à petites cellules (CPPC), est la forme de cancer la plus répandue en Amérique du Nord. Le CPPC donne souvent lieu à des rechutes, d'où un taux de survie de 3 à 8 % au bout de cinq ans. Le sombre pronostic de la maladie est en partie attribuable à son diagnostic tardif. Les syndromes paranéoplasiques peuvent être des manifestations précoces du CPPC. Les avantages possibles d'un diagnostic précoce a poussé les chercheurs à trouver des marqueurs de la maladie. Certains patients peuvent présenter surtout des symptômes de dysmotilité gastro-intestinale, sans cause apparente. La recherche d'anticorps anti-Hu comme marqueur valable de CPPC devrait être envisagée chez ces patients. Voici un cas de CPPC, accompagné d'anticorps anti-Hu, se présentant sous forme de pseudo-obstruction intestinale. Il sera donc question dans le présent article de dysmotilité gastro-intestinale comme manifestation d'un syndrome paranéoplasique.

Department of Medicine, University of Toronto, and University Health Network and Mount Sinai Hospital, Toronto, Ontario
Correspondence and reprints: Dr David N Moskovitz c/o Dr Kenneth V Robb, 399 Bathurst Street, 8 East #514, Toronto, Ontario M5T 2S8. Telephone 416-603-6467
Received for publication October 4, 2001. Accepted January 18, 2002

Paraneoplastic syndromes result from the distant effects of underlying malignancy, and are not related to the local effects of the primary tumour or its metastases. Paraneoplastic neurological syndromes may affect any part of the nervous system. The most common neurological syndromes are paraneoplastic sensory neuropathy and paraneoplastic encephalomyelitis (1). Other manifestations include cerebellar ataxia, limbic encephalitis, polyradiculopathy, associated Lambert-Eaton myasthenic syndrome, myopathy and a multitude of gastrointestinal syndromes including gastroparesis, pseudo-obstruction, esophageal achalasia and other dysmotilities. The onset of these paraneoplastic syndromes typically precedes tumour diagnosis. Seropositivity for type 1 antineuronal nuclear autoantibodies (ANNA-1 or anti-Hu antibodies) is a marker of small cell lung carcinoma (SCLC) in patients who present with paraneoplastic symptoms.

A patient whose presenting features were solely or entirely related to gastroparesis is described. The patient tested positive for anti-Hu antibodies, and SCLC was ultimately diagnosed.

CASE PRESENTATION

A 57-year-old woman with a six-month history of weight loss was transferred to the authors' facility for further investigations. She was previously well, with no specific gastrointestinal illnesses. Past medical history was significant for Graves' disease, which had been treated with thyroidectomy and thyroid replacement therapy. Her thyroid disease was under control. Diabetes was not present. Her medications on transfer included thyroxine 0.05 mg taken orally once a day, docusate sodium 100 mg taken orally bid, domperidone 20 mg taken orally with meals, lactulose 30 mL taken orally each night, dimenhydrinate 25 to 50 mg taken intravenously or intramuscularly every 4 to 6 h as required and metoclopramide 5 mg taken intravenously every 6 h. The patient had a 40 pack-year history of smoking. She did not consume any alcohol. She had lost 23 kg of body weight, associated with severe constipation, nausea and vomiting, and she eventually became intolerant to oral foods. Further questioning revealed a several month history of a sensory neuropathy with glove and stocking distribution. She denied any fever. The rest of the functional inquiry was unremarkable. Physical examination revealed cachexia, with marked temporalis wasting. Her heart rate was 84 beats/min, blood pressure 130/60 mmHg, respiratory rate 16 breaths/min, temperature 36.1°C and oxygen saturation 97% on room air. Cardiac and respiratory examinations were normal. There was no clubbing, and there were no bowel sounds. The abdomen was soft and nontender, with no hepatosplenomegaly or masses. Cranial nerves 2 to 12 were normal. Motor examination revealed no focal abnormalities, other than some general weakness likely related to her cachexia. Reflexes were equal bilaterally, and there was normal tone. Sensory examination showed decreased sensation to light touch, pin-prick, and vibration in the arms and legs bilaterally. Coordination was normal. There was no other clinical evidence of autonomic neuropathy. Investigation in hospital revealed that her thyroid function was normal. The chest x-ray was normal. Gastric motility studies demonstrated severely delayed gastric emptying, with a half-time of greater than 293 min. After trying multiple gastric motility agents, she finally required total parenteral nutrition. Electromyography studies confirmed a diffuse sensory polyneuropathy. A computed tomography scan of the thorax showed enlarged hilar lymph nodes with normal lung parenchyma. Mediastinoscopy with subcarinal node biopsy revealed small cell anaplastic carcinoma. Tests from the laboratory at the University of Arkansas Medical Services, Fayetteville, were positive for anti-Hu (antineuronal nuclear antibodies). Two serum samples from the patient were examined by immunohistochemistry, Western blot of purified human neuronal proteins and Western blot of HuD recombinant protein. The techniques used were similar to those reported by Szabo et al (2). All tests were positive for anti-Hu antibodies, and all assays were done using sera dilutions of 1:1000. The patient remained resistant to the concurrent use of two antiemetics (dimenhydrinate, prochlorperazine), two motility agents (metoclopramide, domperidone), one stool softener (docusate sodium) and one anticholinesterase agent (pyridostigmine bromide), and required ongoing total parenteral nutrition. She was transferred to a local cancer centre to receive definitive chemotherapy for her SCLC. The patient was started on a chemotherapy combination of carboplatinum and etoposide. There were no complications of the chemotherapy treatment. She was continued on chemotherapy treatment and a three-week course of local radiation treatment. After five months of follow-up, there had been no change in her clinical status.

DISCUSSION

Paraneoplastic syndromes are disorders that result from the distant effects of an underlying malignancy, and are not related to the local effects of the primary tumour or its metastases. In the majority of patients with gastrointestinal manifestations, the evolution of symptoms and signs is subacute (less than six months). Reports of symptoms developing over 24 h, however, have been documented, the mean latency between presentation and tumour diagnosis being between eight and 12 months (3). Gastroparesis and intestinal pseudo-obstruction are known manifestations of the paraneoplastic syndrome associated with SCLC (4). The most common gastrointestinal manifestations of the paraneoplastic syndrome are reported in Table 1 (3). It is important to recognize gastrointestinal symptoms because they precede oncological diagnosis and are the presenting symptoms in the majority of cases. Dysmotility syndromes are often accompanied by other paraneoplastic manifestations. Most commonly, patients present with neuropathy (40%) (sensory, mixed somatic, autonomic, motor). Cerebellar symptoms (10% to 20%), limbic encephalitis (10% to 20%) (seizures, cognitive disturbance), cranial neuropathies (15%), myelopathies (2%), myopathies (5%) and associa-

tions with the Lambert-Eaton syndrome (5%) have been reported. SCLC is the usual neoplasm associated with the syndrome of paraneoplastic chronic intestinal pseudo-obstruction (5,6). In one study of 162 patients identified as being anti-Hu positive, 81% had SCLC (3). However, there have been reports of paraneoplastic syndromes with renal cell carcinoma, prostate carcinoma, breast carcinoma, bladder carcinoma, ovarian carcinoma, choroid papilloma, lymphoma and cervical carcinoma (3,7,8).

The association of anti-Hu and pseudo-obstruction was demonstrated in 1993 (9). Since then, studies have shown an association between anti-Hu and other gastrointestinal manifestations, including gastroparesis, esophageal achalasia and dysphagia (3). In one study (3), the investigators looked at the spectrum of symptoms and signs in adults with cancer who were positive for anti-Hu antibodies; 19 of 162 patients (12%) initially presented to their gastroenterologist with symptoms of gut dysmotility. In all cases, SCLC was ultimately diagnosed. In the same study, 38 patients (23%) developed gastrointestinal dysmotility over the course of their illness. This study concluded that, for the clinical gastroenterologist, paraneoplastic autoimmune serological testing offers a valuable diagnostic aid for determining the likelihood of an underlying SCLC in patients presenting with unexplained gastrointestinal dysmotility disorders. These results are consistent with our presented case. While not available in Canada, measurement of antibodies is available at centres in the United States, including the Mayo Clinic and University of Arkansas. More recently, one study suggested a high seropositivity of serological testing for the diagnosis of an underlying malignancy in the absence of negative imaging studies (10). Lee et al (10) suggested that positive serological testing including ANNA-1, type 1 Purkinje cell cytoplasmic antibody or N-type calcium channel binding antibodies (all different terms for various forms of anti-Hu antibodies) in patients with unexplained gastrointestinal symptoms should prompt further evaluation for a malignant process. It can be concluded that a panel of paraneoplastic serological tests serves as a useful initial step in patients with a high clinical suspicion.

The principle Hu antigens in humans are HuD, HuC, and Hel-N1. Hu antigens are 35 to 40 kD proteins expressed both in the nucleus and in the cytoplasm of all neurons of the central and peripheral nervous system, as well as in tumour tissue (11). The antibody received the name Hu from the first two letters of the original index patient's last name. The function of Hu proteins is unknown; however, it has been postulated that they act as transfactors involved in selective mRNA degradation and promote differentiation of the neuronal phenotype (12). The two assays for the detection of Hu antibodies include immunohistochemistry (13) and Western blot analysis (14). One study reported a specificity of 99% and a sensitivity of 82% in detecting paraneoplastic syndromes (15). One study (16) found a 10% rate of false-positive anti-Hu results using immunohistochemistry. The titres of Hu antibodies have been shown to correlate with the presence of paraneoplastic syndrome. Titres greater than 1:1000 are associated with paraneoplastic syndromes (12).

TABLE 1
Common gastrointestinal manifestations of the paraneoplastic syndrome

Symptom	Rate of occurrence (%)
Gastroparesis	50
Pseudo-obstruction	21
Dysphagia	11
Esophageal achalasia	11
Pyloric stenosis	5
Anal spasticity	3

Data from reference 3

The pathogenesis of paraneoplastic neurological syndromes is incompletely understood. One hypothesis explaining paraneoplastic visceral neuropathy is infection. Another more plausible mechanism of pathogenesis is autoimmunity. Studies have demonstrated antibodies to neural tissue in the sera of patients with SCLC who experienced paraneoplastic symptoms (17-21). Tumour-associated antigens found in or on the surface of human SCLC cells, but not on normal lung tissue, cross-react with normal nervous system tissue. Examples include autoantibodies to the nuclei of neurons of dorsal root ganglia in patients with SCLC having subacute sensory neuropathy. It has also been hypothesized, through embryological studies, that all amine precursor uptake and decarboxylation cells of the bronchopulmonary and gastroenteropancreatic axis have a common origin (22-25). It has, therefore, been suggested that neural tissues and SCLC that share a common embryological origin have the potential to express similar antigens. As a result, an immune cell response to the tumour could cross-react with the central, peripheral and enteric nervous systems. If localized to the myenteric plexus, gastrointestinal motor dysfunction would be the primary manifestation. Finally, there is circumstantial evidence to suggest that T cell-mediated mechanisms play a major pathogenic role. This is suggested by the inflammatory infiltration of mononuclear cells in areas of the nervous system that are symptomatic.

Unfortunately, the management of patients with SCLC and paraneoplastic syndrome has been difficult. The use of steroids, plasma exchange and intravenous immunoglobulin has been found to be unsuccessful (3). The hypothesis that the gastrointestinal manifestations associated with the paraneoplastic syndrome are caused by an autoimmune process has prompted the use of immunosuppressants. While there have been reports of improvement with intravenous immunoglobulin therapy, the general response has been poor. There have been documented responses to treatment with chemotherapeutic agents (26). In general, the treatment of the gastrointestinal manifestations focuses on treating the primary malignancy (27). However, there have

been no reports showing improvement with the treatment of the underlying SCLC. Therefore, the management of gastrointestinal symptoms is mainly supportive. Management focuses on nutrition, prokinetic agents and consideration for surgery. Oral or enteral nutrition is typically used for neuropathic disorders, while parenteral nutrition may be necessary in patients with severe dysmotility. Prokinetic agents include erythromycin, metoclopramide, octreotide, neostigmine and 5-hydroxytryptamine$_4$ agonists. A surgical role in intestinal dysmotility is predominantly to resect or bypass localized disease.

SUMMARY

SCLC typically presents at an advanced stage with large hilar masses and mediastinal adenopathy. Patients can present earlier with a paraneoplastic syndrome. The most common neurological syndromes associated with SCLC are paraneoplastic sensory neuropathy and encephalomyelitis. Though less common, patients may present with predominantly gastrointestinal symptoms, as in our patient. A significant unexplained gastroparesis should prompt the physician to consider anti-Hu antibodies and SCLC.

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