Paraneoplastic intestinal pseudo-obstruction, mononeuritis multiplex, and sensory neuropathy/neuronopathy

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A patient with diffuse intestinal pseudo-obstruction consisting of gastric paresis and impaired small and large bowel motility, mononeuropathy multiplex, and sensory neuropathy/neuronopathy was found to have small-cell carcinoma of the lung. The clinical symptoms were thought to be consistent with paraneoplastic neuropathy, and high antineuronal and anti–calcium channel antibodies led to the diagnosis of small-cell carcinoma of the lung. Identification of paraneoplastic neuropathy is important, because early treatment may halt the progression of the underlying carcinoma.

(Key words: Mononeuropathy multiplex, paraneoplastic neuropathy/neuronopathy, intestinal pseudo-obstruction, intestinal motility, small-cell carcinoma of lung)

Neurologic paraneoplastic syndromes have varied clinical manifestations and several distinctive antineuronal autoantibodies that are associated with various types of cancer. These antineuronal autoantibodies include anti–Purkinje cell cytoplasmic antibodies, which are a marker of gynecologic and breast carcinoma in the context of subacute cerebellar degeneration; anti–calcium channel antibodies, which are found in Eaton-Lambert syndrome (most frequently a marker in lung carcinoma); and antineuronal nuclear antibodies, which are found in patients with small-cell carcinoma (SCC) and associated with peripheral neuropathies and encephalomyeloradiculopathies. In the case we report here, a patient had paraneoplastic intestinal pseudo-obstruction with presumed involvement of the myenteric plexus and findings suggestive of a mononeuritis multiplex and sensory neuropathy/neuronopathy. Antineuronal autoantibodies served as a distinctive marker, leading to the discovery of SCC, which initially responded to chemotherapeutic treatment.

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Report of case

A 65-year-old woman had acute onset of left lower quadrant abdominal pain, a 40-pound weight loss during a 4- to 6-week interval, hypotension, hyponatremia, and a rigid abdomen with rebound tenderness. The patient had no previous medical care since 1963. Surgery revealed a perforated sigmoid colon, and she subsequently underwent left hemicolectomy, sigmoid colon resection, and diverting colostomy. After surgery, the patient received antibiotics intravenously. No evidence of bowel sounds was found, substantial abdominal distention developed, and total parenteral nutrition (TPN) was begun. Pathologic evaluation of the resected colon showed absence of ganglion cells, consistent with visceral myopathy-neuropathy.

Initial neurologic evaluation revealed no focal or lateralizing deficits but showed evidence of encephalopathy secondary to sepsis and hypotension. Computed tomography (CT) of the brain revealed a left internal capsule and right occipital lobe infarct. A left visual field deficit abruptly developed, followed by respiratory distress, which led to ventilatory support. Her mental status and level of consciousness deteriorated, which was attributed to laminar infarcts secondary to hypoxia. Neurologic examination, however, continued to show no focal or lateralizing deficits.

Because the patient had no return of bowel sounds and progressive abdominal distention, a return to the surgical suite was necessary. A diffuse intestinal pseudo-obstruction including gastroparesis, marked small and large intestinal dilation, and poor colonic propulsive activity was found. Evaluation of muscle and sural nerve biopsy specimens obtained at the time of surgery revealed type II atrophy and loss of large myelinated fibers, with several fibers undergoing wallerian degeneration. There was no evidence of vasculitis or inflammation.

At subsequent neurologic examinations, the patient continued to be dysautonomic, with absence of intestinal motility, absence of sweating, stocking-glove paresthesias, arreflexia, and orthostatic hypotension. Extensive electromyography 5 weeks after admission revealed absent sensory nerve action potentials, asymmetric motor-evoked amplitudes, prolonged conduction velocities and F-responses, and no decremental response to repetitive nerve stimulation. Needle electromyography demonstrated asymmetric multifocal denervation, along with reinnervation. The impression was mononeuropathy multiplex superimposed on a sensory neuronopathy and an autonomic neuropathy.

Table 1
Differential Diagnosis of Sensory Neuropathy

- **Toxicity**
  - Doxorubicin (Adriamycin)
  - Cisplatin (Platinol)
  - Paclitaxel (Taxol)
  - Metronidazole
  - Penicillin
  - Vincristine sulfate (Oncovin)
  - Hypervitaminosis B_6
  - Bepridil hydrochloride (Vascor)
- **Vitamin deficiency**
  - Vitamin B_{12}
  - Vitamin E
- **Collagen or vascular disorder**
  - Sjögren's syndrome
  - Mixed connective tissue disease
  - Scleroderma
  - Friedreich's ataxia
  - Fabry's disease
- **Infection**
  - Tabes dorsalis
  - Human immunodeficiency virus
  - Diphtheria
- **Other**
  - Paraneoplastic sensory neuronopathy
  - Acute inflammatory neuropathy
  - Paraproteinemic neuropathy (IgM-κ)

Sensory neuropathy (*Table 1*), mononeuritis multiplex (*Table 2*), pseudo-obstruction, progressive dysautonomia, weight loss, and lack of vasculitis or inflammation at evaluation of muscle and nerve biopsy specimens suggested the possibility of a paraneoplastic syndrome. Laboratory studies revealed increased antinuclear neuronal type I (anti-Hu) antibodies at 1:960 and anti-calcium channel antibodies. Antinuclear neuronal type II antibodies and anti–Purkinje cell antibodies were not found. The high autoantibody titer suggested an associated SCC. A CT scan of the chest showed a 3 × 6 × 4-cm left hilar mass and bilateral pleural effusions. Lung biopsy confirmed the SCC.

The patient subsequently underwent chemotherapy and continuous TPN secondary to lack of return of intestinal motility. The patient slowly became more lucid but remained ventilator dependent. The patient's subsequent medical course was complicated by hypotension, tachyarryhthmias, and inability to be weaned from the ventilator. Initiation of chemotherapy led to a decrease in the lung mass. The patient was eventually discharged to an extended-care facility 12 weeks after admission, but unfortunately, she died 2 months later.

Table 2
Differential Diagnosis of Mononeuritis Multiplex

- **Ischemic neuropathy**
  - Vasculitic neuropathy associated with connective tissue disease
  - Vasculitic neuropathy with other associated cause
  - —Remote effect of malignancy
  - —Hypersensitivity
  - Nonsystemic vasculitic neuropathy
  - Neuropathy due to diabetic microangiopathy
  - Neuropathy due to amyloid vasculopathy
  - Neuropathy due to atherosclerotic vascular disease
- **Demyelinating neuropathy**
  - Acute inflammatory demyelinating polyradiculoneuropathy (Guillain Barré syndrome)
  - Chronic inflammatory demyelinating polyradiculopathy
  - Paraproteinemic demyelinating polyneuropathy
  - Hereditary liability to pressure palsy
  - Inflammatory demyelinating polyneuropathy associated with human immunodeficiency virus (HIV)
- **Infectious neuropathy**
  - Leprosy
  - Herpes zoster
  - *Borrelia burgdorferi* (Lyme disease)
  - HIV
- **Neuropathy secondary to granulomatous infiltration**
  - Sarcoidosis
  - Sensory perineuritis
  - Lymphomatoid granulomatosis
- **Neuropathy secondary to tumor infiltration**
- **Other**
  - Brachial plexus neuropathy
  - Lumbosacral plexus neuropathy

Discussion

Gastrointestinal symptoms of progressive anorexia, early satiety, vomiting, and constipation are the clinical presentation of paraneoplastic pseudo-obstruction. Patients often have substantial weight

Table 3
Serologic Markers for Small-Cell Carcinoma Chronic Intestinal Pseudo-Obstruction

Clinical-neurologic presentation	Marker	Type	Pathologic features
Pseudo-obstruction alone	Enteric neuronal antibodies	IgG	Binds to neuronal elements in myenteric plexus and submucosal plexus
Pseudo-obstruction Subacute sensory neuropathy Encephalomyeloradiculopathy	Anti–neuronal nuclear antibody type I (anti-Hu)	IgG	Binds to nuclei in cerebellum, peripheral nervous system, and myenteric plexus
Pseudo-obstruction Eaton-Lambert syndrome	Anti–calcium channel antibody	IgG	Binds to voltage-gated calcium channels

loss and abdominal pain, as well as a history of abdominal surgery.[1] After weeks to months, paresthesias of the distal extremities begin, progressing to severe peripheral neuropathy (mononeuritis multiplex, sensory neuropathy) with weakness, postural instability, and urologic symptoms. Most patients have evidence of peripheral or autonomic symptoms, and some have involvement of both.

The differential diagnosis of pseudo-obstruction relates to any disorder of intestinal motility. These include true obstruction, visceral myopathy, inclusion-body myenteric plexopathy, and familial autosomal dominant pseudo-obstruction. Secondary causes include connective tissue disease (myositis, scleroderma, lupus, and amyloidosis), endocrine disorders (hypothyroidism, diabetes, hyperparathyroidism), medications (anticholinergic side effects), and neurologic disorders that affect the autonomic nervous system (Shy-Drager syndrome).[2]

The association of autonomic instability and paralysis of the gastrointestinal tract with SCC has long been known. In 1975, Ahmed and Carpenter[3] described a patient with tumor infiltration (small cell) into autonomic nerves, especially in the myenteric plexus. Lhermitte and associates,[4] in 1980, suggested a paraneoplastic syndrome in a patient with SCC and myenteric plexopathy. An autoimmune cause was then suggested by Schuffler and colleagues[5] in 1983 in a patient with chronic pseudo-obstruction and subsequent progressive autonomic dysfunction. Sodhi and coworkers[6] then reported abnormal parasympathetic-sympathetic autonomic testing results in two patients with intestinal pseudo-obstruction and SCC of the lung.[6] Chinn and Schuffler[1] reported an additional seven patients with pseudo-obstruction, myenteric plexopathy, and dysautonomia. These patients had neurologic symptoms of encephalopathy, ataxia, neurogenic bladder, and peripheral neuropathy after their abdominal symptoms. Diagnosis of cancer lagged 4 to 26 months after the onset of symptoms in six of these seven patients (symptoms followed the diagnosis of SCC in one case), and five of the seven patients died within 9 months of onset of chronic pseudo-obstruction.

Chronic intestinal pseudo-obstruction as a paraneoplastic syndrome has recently been further supported by certain autoantibodies that serve diagnostically as useful serologic markers for the presence of SCC (*Table 3*). First, enteric neuronal antibodies of the IgG type have been found to bind to neuronal elements in the myenteric plexus and submucosal plexus of patients with SCC and pseudo-obstruction, but not in patients with SCC alone.[7] These antibodies bind selectively to nuclei and cytoplasm of neuronal elements in the intestines and probably reflect expression of the tumor of an antigenic determinant found in enteric neurons. Second, antineuronal nuclear antibodies (also known as Hu antibodies) are found in patients with SCC and associated subacute sensory neuropathy/neuronopathy and encephalomyeloradiculopathies.[8] These antibodies contrast with Ri antineuronal nuclear antibodies found in patients with breast cancer[9] and anti–Purkinje cell cytoplasmic antibodies (also known as Yo) in patients with cerebellar ataxia.[10-15] Antineuronal nuclear autoantibodies, also of the IgG type, bind to nuclei (less so to cytoplasm) in the central nervous system, especially the cerebellum, the peripheral nervous system, and the myenteric plexus. That the autoantibodies bind both to cerebellum and enteric neurons makes these antibodies not specific to neurons and reflects an immune response that is directed against neuron-related epitopes expressed in the tumor cells. Third, anti–calcium

channel antibodies, again of the IgG type, bind to voltage-gated calcium channels in patients with Eaton-Lambert syndrome and SCC of the lung.[16,17] Again, these autoantibodies suggest expression of antigenic determinant by tumor cells and neurons.

The appearance of multifocal mononeuropathies and paraneoplastic syndrome is controversial, although peripheral vasculitis with a resultant mononeuritis multiplex has been associated with SCC of the lung and renal cell carcinoma.[18] In 1993, Liang and colleagues[19] reported a case of mononeuritis multiplex, sensory neuronopathy, and pseudo-obstruction in a patient subsequently found to have SCC of the lung. The pathogenesis of the neuropathy was unknown, and antineuronal nuclear antibodies served as the diagnostic marker leading to the search for SCC of the lung. As in the case of this report, no pathologic evidence of vasculitis could be found, and mononeuritis multiplex demonstrated electromyographically did not establish the association with the underlying neoplasm. Paraneoplastic pseudo-obstruction, though, has been associated with paraneoplastic sensory neuropathy/neuronopathy and encephalitis.

Paraneoplastic pseudo-obstruction secondary to SCC should be identified as early as possible so that treatment can be initiated. Treatment may halt the progression of the dysautonomia, although reversal of symptoms is uncommon. Symptomatic therapy of pseudo-obstruction with TPN is often the only effective treatment; pharmacologic agents that stimulate bowel activity are ineffective. Rarely, a patient may regain intestinal motility, and trials of oral feedings may be indicated in these individuals.

The prognosis for patients with paraneoplastic pseudo-obstruction is poor on the whole, but possibly somewhat better if the diagnosis of SCC is reached and treated early. Most patients die within 1 year after the onset of gastrointestinal and neurologic symptoms, but several reports have described patients who have gained some return of gastrointestinal function but no neurologic function.[1,6]

This would be the second case reported in the literature, the first having been reported by Liang and coworkers[19] in 1993.

Comment

We have reported the second case of pseudo-obstruction, mononeuritis multiplex, and sensory neuronopathy in a patient who was subsequently found to have SCC of the lung. The association of the intestinal dysmotility, sensory neuropathy/neuronopathy, and antineuronal nuclear antibodies prompted the search for malignancy. Treatment led to initial clinical improvement with disruption in the progression of the dysautonomia, indicating the importance of early identification of the malignancy.

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