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CASE REPORT

Autonomic Function and Motility in Intestinal Pseudoobstruction Caused by Paraneoplastic Syndrome

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Chronic intestinal pseudoobstruction (1) is characterized by nausea, vomiting, early satiety, abdominal discomfort, weight loss, and altered bowel movements that are the consequence of abnormal gastrointestinal motility. The syndrome may result from a number of diseases extrinsic to the gut (eg, disorders at any level of the brain–neural axis) or from an isolated degeneration of neurons in the myenteric plexus. A viral etiology has been postulated in some cases, and cytomegalovirus has been identified in the myenteric plexus of a few patients with chronic intestinal pseudoobstruction (2). The syndrome results in considerable morbidity and mortality, and the identification of an underlying condition is of potential importance, particularly if it proves treatable.

We present here two cases of chronic intestinal pseudoobstruction of unusual etiology. These case studies illustrate the use of gastrointestinal motility (3) and autonomic assessment (4) in the investigation of patients with symptoms suggestive of a motility disturbance of the proximal gut (5).

CASE REPORTS

Patient 1. A 53-year-old, white male presented to the Mayo Clinic in January 1988 with a five-month history of nausea, vomiting, and severe constipation following a "flulike" illness. After the onset of these symptoms in September 1987, he was evaluated at the first outside hospital. An initial abdominal radiograph suggested a small bowel obstruction, but an upper gastrointestinal series, gastroscopy, colon x-ray, abdominal ultrasound, and CT scan were unrevealing. The patient was treated with nasogastric suction with improvement and was discharged. One month later, he was readmitted with recurrent small bowel obstruction. An exploratory laparotomy was performed with negative findings, and a normal appendix was removed. He was then transferred to a university medical center for assessment. Further tests, including a total thyroxine, antinuclear antibody, and rectal biopsy for amyloid were unremarkable. Neurological examination was considered normal. Motility studies revealed uncoordinated esophageal contractions and delayed gastric emptying (18% of a ^{99m}Tc-radiolabeled egg meal emptied at 90 min). In view of an unsatisfactory response to metoclopramide, he was started on central parenteral nutrition three weeks prior to transfer here.

At initial interview at the Mayo Clinic, the patient reported a 70-pound weight loss over the previous five months, nausea, anorexia, and dysphagia of recent onset. He also described extreme fatigue, necessitating bedrest, and recurrent vomiting of undigested food up to 48 hr after ingestion; bowel movements occurred once every 14 days. Review of symptoms was positive for dysgeusia, impaired ejaculation but normal penile erection, dyspnea on exertion, orthostatic dizziness, and cold intolerance. His past history included several years of hypertension, 60 pack-years of cigarette smoking, and consumption of six cans of beer per day.

Physical examination was remarkable for an emaciated male, with a normal temperature, pulse rate of 60/min, and blood pressure 130/84 mm Hg while recumbent. The standing pulse rate was 84/min and blood pressure 110/20 mm Hg. A right subclavian catheter was in place. The chest was clear to auscultation. The abdomen was normal except for a transverse lower abdominal scar from his previous laparotomy. There was no succussion splash or abdominal distension. Neurological examination was nor-

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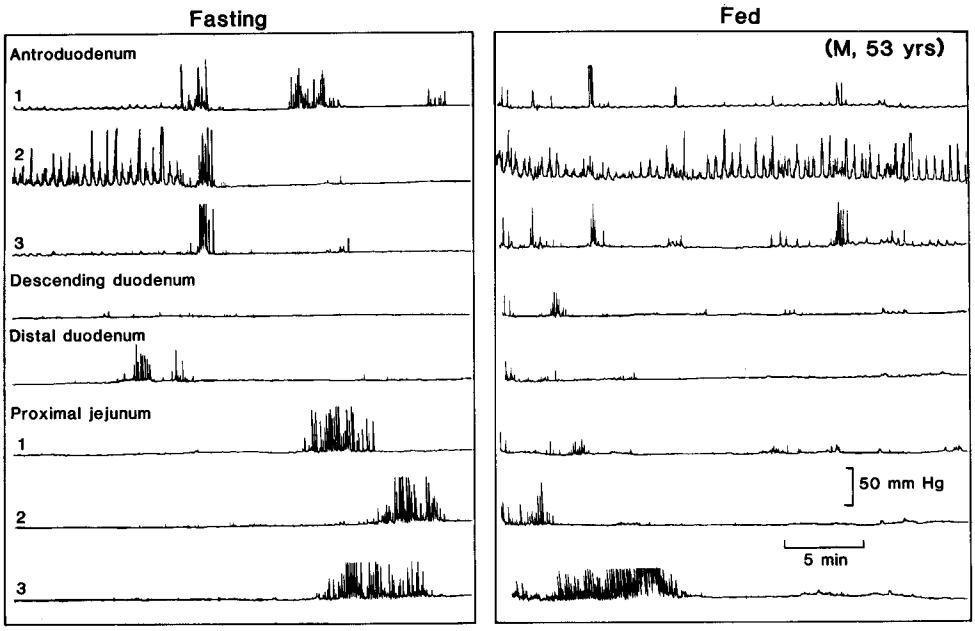

Fig 1. Upper gastrointestinal motility tracing showing uncoordinated fasting and postprandial activity. In the fasting record, note the abnormal propagation of clustered pressure activity in the proximal jejunum, where the cluster at level 3 occurs simultaneously with level 1 (20 cm proximal to it), and approximately 3 min before that in level 2 (10 cm proximal to it). In the postprandial record, note the paucity of distal antral contractions (antroduodenum 1); prominent pyloric activity (antroduodenum 2); hypomotility in the duodenal bulb (antroduodenal 3), descending and distal duodenum, and proximal jejunum (1 and 2); and the uncoordinated high-amplitude cluster of phasic pressure activity in the most distal jejunal manometric tracing obtained.

mal except for diminished reflexes and distal sensory loss in the lower extremities.

Routine laboratory evaluations were unremarkable and, in particular, serum potassium, morning and midnight cortisol levels, and full hematologic and biochemical profiles were negative. The chest x-ray was normal, and supine abdominal radiographs demonstrated dilated loops of small bowel.

Review of gastrointestinal contrast imaging and abdominal ultrasound and CT scans performed elsewhere was noncontributory. As there was no evidence of mechanical bowel obstruction, a gastrointestinal motility study was performed for 3 hr during fasting and for 2 hr after ingestion of a 535-calorie standardized solid–liquid meal (3). This motility study was abnormal, showing no normal interdigestive migrating motor complexes during fasting. Postprandially, there was hypomotility of the antrum, in sharp contrast to pronounced pylorospasm (Figure 1). In the small intestine, clusters of uncoordinated phasic pressure activity were superimposed on motor quiescence. These features were suggestive of either an extrinsic or intrinsic neuropathy of the gut.

To determine whether there was neuropathy affecting organs other than the gastrointestinal system, other tests of autonomic function were performed. Fractionated orthostatic catecholamines were normal in lying and standing positions; a thermoregulatory sweat test (TST) revealed anhidrosis of 42% of the body surface affecting the medial forehead, lower trunk, lower extremities, and distal hands; the distribution suggested a pre- and/or postganglionic sympathetic lesion. The Quantitative Sudomotor Axon Reflex Test (QSART) was normal in the forearm and reduced but not absent in the foot (sweat output = 0.55 $\mu l/cm^2$, normal 0.92–5.73). The combined TST and QSART results indicated that although some postganglionic autonomic failure was present, a preganglionic or central component was possible. The normal serum supine norepinephrine and the normal release of norepinephrine and epinephrine in response to an intravenous bolus of edrophonium [Tensilon® (6)] (Figure 2) excluded widespread postganglionic sympathetic vasomotor failure. The normal cardiovascular vagal reflexes and orthostatic heart rate and blood pressure responses suggested partial or focal rather than generalized autonomic failure with preservation of lower brain-stem autonomic reflex pathways. Overall, the autonomic function assessments suggested partial postganglionic failure with the possibility of a focal, central, or preganglionic lesion as well.

A magnetic resonance imaging scan of the head and cervical spine was, therefore, performed and showed a mass lesion in the midbrain, obstructive hydrocephalus, and two parietal lobe lesions, suggesting metastatic disease to the central nervous system (Figure 3). Search for the primary cancer yielded a left hilar mass on CT scan of the chest (Figure 4). Tissue obtained by mediastinoscopy revealed an anaplastic small cell cancer.

The patient received whole-brain radiotherapy for the cerebral metastases and was started on chemotherapy with cisplatin, doxorubicin, cyclophosphamide, and etop-

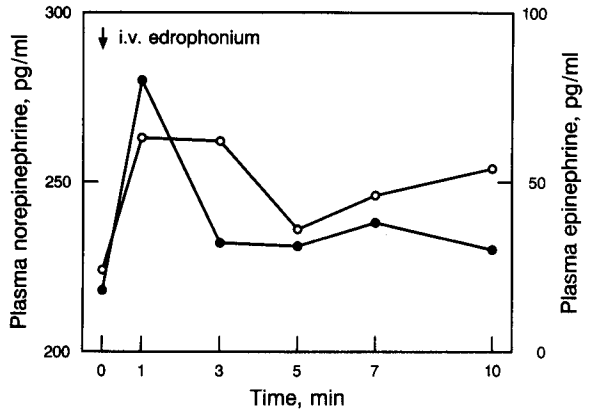

Fig 2. Profile of plasma norepinephrine (open circles) and epinephrine (closed circles) in response to intravenous injection of 1 mg edrophonium; note the prompt rises in both catecholamine levels, suggesting postganglionic sympathetic pathways are normal (see Discussion).

oside. He tolerated the chemotherapy poorly, and in spite of dose reductions was hospitalized after each cycle for infections associated with neutropenia. After four cycles of chemotherapy, repeat CT scans of the brain, chest, and abdomen revealed no evidence of tumor. He remained on total parenteral alimentation with unabated symptoms until his death 13 months later.

Patient 2. A 60-year-old Caucasian female first presented to Mayo Clinic in May 1987, with a year's history of dysphagia, heartburn, upper abdominal discomfort,

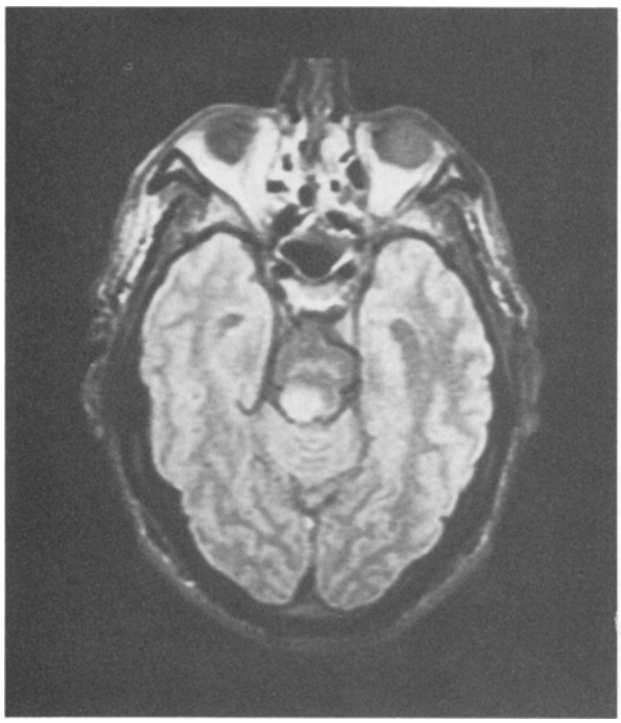

Fig 3. Magnetic resonance imaging of the head showing a lesion in the midbrain (arrow).

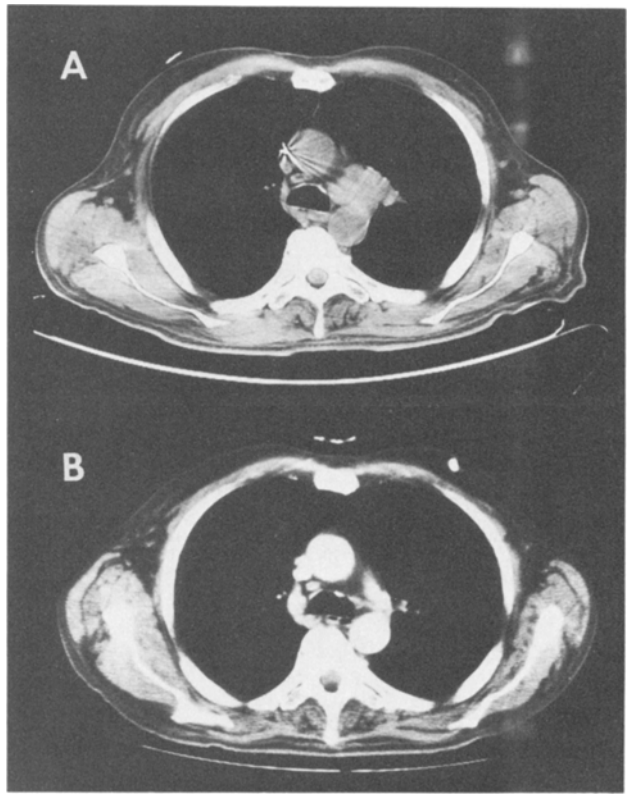

Fig 4. Computerized tomography of the chest showing (A) left hilar adenopathy (arrow), and (B) shrinking of the hilar mass following chemotherapy (arrow).

nausea, vomiting, bloating, distension, and constipation. She had smoked about 10 cigarettes per day for 40 years and underwent laparotomy elsewhere in January 1987, when cholecystectomy, partial pancreatectomy, and splenectomy were performed for cholelithiasis and suspected chronic pancreatitis, which was not proven histologically. Physical examination revealed Adie's phenomenon in the right pupil, well-healed abdominal scars, abdominal distension, and increased bowel sounds. There was no abdominal succussion splash or other abnormality noted on the remainder of the physical and neurological examinations. Investigations revealed normal barium contrast studies of the entire gut; motor incoordination of the esophagus was detected on an upper gastrointestinal series and manometric studies showed abnormalities in the propagation of deglutition waves through the esophagus following wet swallows. Upper gastrointestinal endoscopy was normal. An intestinal motility study demonstrated uncoordinated, prolonged clusters of phasic pressure activity in the duodenum during both fasting and fed phases. Scintigraphic gastric emptying of solids and liquids was delayed [$t½$ radiolabeled egg 200 min (laboratory controls 132 ± 35, SD), $t½$ radiolabeled milk 80 min (laboratory controls 42 ± 13, SD)]. She was reassessed during symptomatic treatment during the next year because of persistent symptoms; no weight loss was recorded during this period.

Repeat motility studies of the upper gut revealed persistent, uncoordinated duodenal pressure activity during fasting, and antral hypomotility and propagated intestinal clusters postprandially. The amplitude, frequency of contractions, and propagation velocity of the postprandial clusters were similar to those of phase III of the interdigestive migrating motor complexes. Autonomic reflex screen showed evidence of both sympathetic and parasympathetic postganglionic neuropathy: mild orthostatism (BP lying 116/70, standing 96/64 mm Hg); abnormal heart period responses to Valsalva maneuver (Valsalva ratio 1.24, normal >1.45), and deep breathing (4, normal >12). Fractionated plasma catecholamines were normal supine and standing. Studies searching for the cause of autonomic neuropathy were unrewarding; these included search for amyloidosis and chest x-rays taken in May 1987 and June 1988.

In December 1988, she presented with a three-week history of cough, sputum, malaise, upper back pain, and worsening of the dysphagia, nausea, and abdominal discomfort. A chest x-ray revealed a soft tissue 2-cm-diameter mass lesion under the aortic arch; CT scan of the chest showed a 4 × 4 × 8-cm mediastinal mass extending from the pulmonary outflow tract to the level of the left brachiocephalic vein, and left hilar and subcarinal lymphadenopathy. A single, hard, 1-cm-diameter, supraclavicular node was subjected to needle aspiration biopsy and revealed metastatic small cell undifferentiated carcinoma. Computerized tomographic examinations of the abdomen and head were negative. The patient died six months after the diagnosis.

DISCUSSION

These case studies illustrate the importance of considering a disorder of the extrinsic neural control of gut motility in any patient who presents with features suggestive of chronic intestinal pseudoobstruction. Although our studies do not prove that the extrinsic neural control of the gut is abnormal, the findings on testing extraintestinal autonomic function suggest involvement of autonomic supply to the gut. An alternative hypothesis is that a parallel disorder of the enteric nervous system causes the motor dysfunction within the gastrointestinal tract, as suggested by others (7). We believe that the former hypothesis is as tenable as the latter.

Although the association between disturbed gut function and disease of extrinsic neural control is well recognized, the strategies for selection of patients for further thorough neurologic evaluation are unclear in the literature. The presence of historical features suggesting autonomic dysfunction, such as postural dizziness, sweating abnormalities, bladder dysfunction, and ejaculatory difficulty, should alert the physician to the need to more thoroughly assess autonomic function. Since dehydration and orthostatism may be secondary to the pseudoobstruction, and these other symptoms may occur more commonly in older patients (eg, impotence), it is our practice to routinely assess autonomic function by means of thermoregulatory sweat tests and autonomic reflex screen in all patients with normal amplitude but uncoordinated intestinal motility on a manometric study.

The diagnostic strategy that has evolved in our practice involves: first, evaluation of gastrointestinal radiographs to exclude mechanical obstruction, mucosal disease, or an infiltrative process affecting gut smooth muscle or supporting connective tissue; second, assessment of gastrointestinal motility to identify features suggestive of a gut neuropathy (3, 8); and third, a stepwise assessment of autonomic function. The latter includes a thermoregulatory sweat test (9), a screen of autonomic vagal and sympathetic reflex responses, and measurement of plasma fractionated catecholamine levels in the supine and standing positions (10). These tests will often indicate whether the neural lesion is pre- or postganglionic (4, 11). This can be confirmed by using the intravenous edrophonium test as suggested by Leveston et al (6). Normal norepinephrine levels suggest normal postganglionic sympathetic fibers, although abnormalities in supine levels (12) and responses to edrophonium may only be detected when there is widespread postganglionic degeneration. If, as in patient 1, autonomic function testing is abnormal, with some evidence suggesting a preganglionic or central lesion, imaging of the brain and/or spinal cord is indicated. In our experience, magnetic resonance imaging is preferable to CT scanning, particularly since it provides excellent views of structures in the posterior cranial fossa (13) and spinal cord that influence gastrointestinal function. In patients with evidence of postganglionic fiber dysfunction, as in patient 2, imaging of the central nervous system is not indicated.

Chronic intestinal pseudoobstruction in association with malignancy was first described by Heneage Ogilvie in 1948 (14). This entity, sometimes known as Ogilvie's syndrome, was initially thought to be due to malignant infiltration of the sympathetic nerves of the gut, resulting in unopposed parasympathetic stimulation. One of Ogilvie's cases was thought possibly to be due to a small cell carcinoma of the lung. Since then several cases of chronic intestinal pseudoobstruction have been described in association with small cell carcinoma. Table 1 summarizes some of the clinical features of

TABLE 1. CLINICAL FEATURES IN REPORTED CASES OF INTESTINAL DYSMOTILITY ASSOCIATED WITH SMALL CELL CARCINOMA*

Reference Number	*Age*	*Sex*	*Initial chest x-ray*	*Constipation/ diarrhea*	*Cramping/ vomiting*	*Orthostatic hypotension*	*Bladder dysfunction*	*CNS metastasis*	*Outcome*
8	59	F	Normal	−/+	+/+	NM	−	(−)by history and exam	alive and well 1 year after chemo and XRT
14	58	M	NM	+/−	+/−	NM	−	(−)by history and exam	dead in 2 weeks
15	65	M	Normal	+/−	−/−	+	−	(−)by history and exam	alive and well 2 years after XRT
16	55	M	Normal	−/−	+/+	+	+	(−)by autopsy	dead
17	58	M	Normal	+/−	+/+	NM	−	(−)by autopsy	dead
18	65	M	Normal	+/−	−/−	+	−	(−)by autopsy	dead in 4 months
19	58	F	Normal	+/−	+/+	+	+	(−)by autopsy	dead in 10 months
7									
Case 1	58	F	NM	+/−	−/+	+	+	CNS dysfunction	dead in 9 months
Case 2	58	F	NM	+/−	−/−	−	−	(−)by history and exam	dead in 5 months
Case 3	72	M	NM	+/−	−/+	+	+	CNS dysfunction	dead in 5 months
Case 5	74	F	NM	+/−	−/+	−	−	(−)by autopsy	dead in 4 months
Case 6	68	F	NM	+/−	−/+	−	−	(−)by history and exam	dead in 5 months
Case 7	62	M	NM	+/−	−/+	−	−	(−)by history and exam	alive with chemo 41 months after CIP onset
Present Case 1	53	M	Normal	+/−	+/+	+	−	(+)by MRI/CT	dead in 13 months
Present Case 2	60	F	Normal	+/−	+/+	+	−	(−)by CT	dead in 6 months

*NM = not mentioned; XRT = radiotherapy; Chemo = chemotherapy.

the reported cases (7, 8, 14–19). Interestingly, in every case the initial chest x-ray was normal, and the diagnosis of malignancy was not made until weeks or months later. Of three patients treated with either chemotherapy or radiotherapy, two showed resolution of their motility disorder several months after beginning treatment. Few centers have reported more than one patient with this rare complication of lung carcinoma (7).

It seems probable that the autonomic derangements in these patients are due to a paraneoplastic effect of the tumor. Except for one of our patients reported here, none of the cases cited in the literature have demonstrated intracranial metastases. In three of four cases (16–19) in which the gut was studied postmortem, there was axonal degeneration and an infiltrate of plasma cells and lymphocytes accompanied by a proliferation of Schwann cells of the myenteric plexuses, much like that seen in other paraneoplastic disorders of the nervous system. Antigens shared by small cell carcinoma and peripheral nerves have been detected, suggesting a potential immune basis for such a paraneoplastic process (19).

The search for and discovery of a central or preganglionic component of the autonomic dysfunction in patient 1 was crucial in making the diagnosis of malignancy. We believe that the strategy outlined in this report may help to select patients with suspected gut dysmotility for further studies such as CT or MRI of the brain. This approach could help avoid unnecessary investigations, including laparotomy. The recognition that the initial chest x-ray is usually normal in patients with small cell lung carcinoma with this syndrome is important because the clinician with a high index of suspicion can justifiably obtain more sensitive tests for lung cancer, such as sputum cytology or CT scans of the chest. This point was illustrated by the developments in patient 2, in whom the etiology of the visceral autonomic derangements could not be identified and chest x-rays taken after an interval of 13 months from first presentation were negative.

Finally, treatment of the underlying malignancy may not be successful in palliating symptoms of gastrointestinal dysmotility, even though tumor shrinkage is achieved, as in patient 1. Nonetheless, some successes in reversal of gastrointestinal symptoms have been recorded in the literature (8, 15) and should be the motivation for considering a therapeutic trial of chemotherapy or radiation therapy in patients afflicted with this disorder.

SUMMARY

This report documents the occurrence of chronic intestinal pseudoobstruction in association with a small cell carcinoma of the lung with evidence of pre- and postganglionic sympathetic dysfunction in one patient with brain metastases, and with sympathetic and parasympathetic postganglionic dysfunction in a second patient. A strategy is outlined for the identification and characterization of disordered neural control of gut motility. This strategy utilizes gastrointestinal motility studies to confirm gut neuropathy, autonomic function tests, and plasma norepinephrine responses to intravenous edrophonium to identify the level of dysfunction. These cases are compared with others in the literature, and the occult nature of these cancers, the spectrum of symptoms suggesting autonomic dysfunction on presentation, and the occasional response of the neurologic deficit to treatment of the malignancy are highlighted.

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