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CASE REPORT

Autoimmune Gastrointestinal Dysmotility Treated Successfully With Pyridostigmine

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Background & Aims: Autoimmune gastrointestinal dysmotility (AGID) is a limited form of autoimmune autonomic neuropathy occurring idiopathically or in a paraneoplastic context. This disorder is considered rare, but is underrecognized as a cause for GI dysmotilities of varying anatomic extent, severity, and duration. We describe the diagnosis and management of an instructive case. **Methods:** A 60-year-old (nondiabetic) woman presented with a 15-year history of severe isolated gastroparesis. Paraneoplastic autoantibody evaluation aided the diagnosis of AGID. This included indirect immunofluorescence (neuronal nuclear and cytoplasmic antibodies), radioimmunoprecipitation assays (neuronal and muscle plasma membrane cation channel antibodies), and enzyme-linked immunosorbent assay (muscle striational antibodies). **Results:** Serologic testing revealed both ganglionic neuronal acetylcholine receptor and N-type voltage-gated calcium channel autoantibodies. This profile was consistent with AGID and, despite the long history, raised the possibility of lung, breast, or ovarian carcinoma or thymoma. An underlying neoplasm was excluded by appropriate investigations. In a 1-month trial of oral pyridostigmine therapy, the patient's GI symptoms improved and her weight stabilized. Pyridostigmine was continued at a low dose, and was supplemented by tegaserod. **Conclusions:** Autoimmune serology is a valuable adjunct to the diagnosis and guide to management of patients with AGID. The favorable response to acetylcholinesterase inhibitors, despite a 15-year history, suggests an immunopharmacologic rather than an inflammatory cytotoxic pathology. Immunomodulatory therapy may not always be required. Of numerous autoantibodies currently recognized as biomarkers of AGID, the ganglionic acetylcholine receptor autoantibody is the only proven pathophysiologic effector. Certain neuronal nuclear and cytoplasmic autoantibodies are highly predictive of an underlying malignancy.

Pathogenic mechanisms affecting gastrointestinal (GI) motility can operate at the level of the central, autonomic, or enteric nervous system, and include traumatic, toxic, metabolic, infectious, degenerative, and autoimmune causes.[1] In a paraneoplastic context, autoimmune GI dysmotility (AGID) is best known as a remote effect of small-cell lung carcinoma[2] or thymoma.[3] The most commonly recognized presentation is a severe dysmotility affecting any part of the GI tract, but it is most striking as pseudo-obstruction. Idiopathic forms of AGID are a manifestation of autoimmune autonomic neuropathy that selectively affects the enteric nervous system.[4] In this report, we describe the stepwise approach to the diagnosis of AGID in a patient who was treated successfully with an acetylcholinesterase inhibitor.

Case Report

A 60-year-old Caucasian woman presented in early 2005 with a 15-year history of progressively worsening postprandial abdominal pain, nausea, and early satiety. She had lost 30 pounds in the preceding 2 years and progressive constipation had developed in the past 6 months.

A radionuclide gastric emptying study performed at another institution revealed delayed gastric emptying (<10% at 2 hours). Results were unremarkable for testing by upper endoscopy, colonoscopy, and small-bowel barium radiography.

Symptoms were not relieved by promotility medications, including metoclopramide, cisapride, erythromycin, and tegaserod (3 mg, 4 times a day). Continued weight loss, despite high-caloric dietary supplements, prompted the patient's referral to our institution for further evaluation.

The patient did not recall a significant antecedent event before the onset of symptoms. Past history included total abdominal hysterectomy and bilateral salpingo-oophorectomy for dysfunctional uterine bleeding. Family history was significant for a maternal grandmother with esophageal cancer and a maternal aunt with gastric cancer.

Previous tests had yielded normal results for fasting plasma glucose, sensitive thyroid-stimulating hormone, antinuclear antibody, and creatinine kinase.

Evaluation at our institution included the following:

1. Gastric and small-bowel emptying (Figure 1) documented 15% of gastric contents emptied at 2 hours, 46% emptied at 4 hours, and 36% of small-bowel contents emptied at 6 hours. These findings were consistent with a moderate delay in gastric emptying and a mild delay in small-bowel transit time. Colonic transit time was within normal limits.
2. Computed tomographic enterography (Figure 2) revealed the stomach to be moderately distended and fluid-filled, without evidence of gastric outlet obstruction.

Abbreviations used in this paper: AAN, autoimmune autonomic neuropathy; AChR, acetylcholine receptor; AGID, autoimmune gastrointestinal dysmotility; CRMP, collapsin response-mediator protein-5; GI, gastrointestinal.

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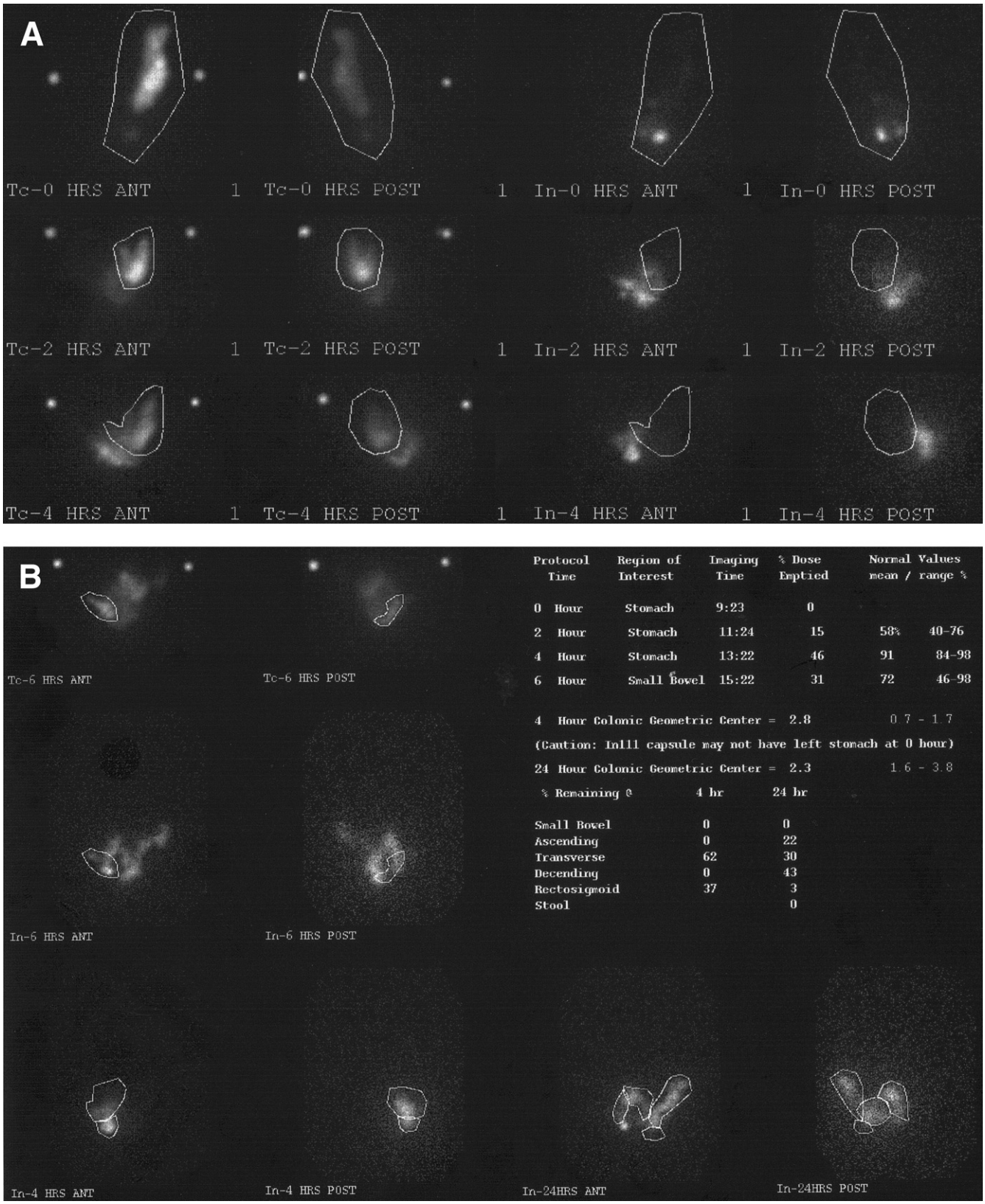

Figure 1. Radionuclide emptying study showed moderate delay in gastric emptying and mild delay in small-bowel emptying.

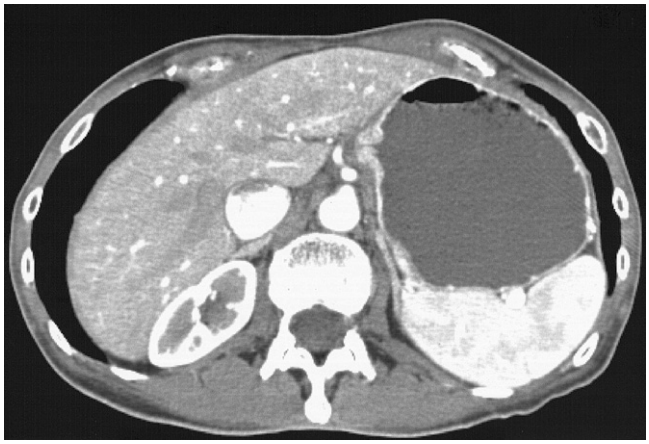

Figure 2. Computerized tomography enterography showed a dilated, fluid-filled stomach.

3. Upper endoscopy was normal. Intrapyloric injection of 100 U botulinum toxin (25 U/quadrant) was performed for empiric treatment of gastroparesis, and the patient subsequently reported mild improvement in symptoms.

Serologic evaluation for paraneoplastic autoantibodies (an algorithmic cascade performed by Mayo Medical Laboratories)[4–8] revealed N-type calcium-channel antibody (92 pmol/L; normal range, ≤20 pmol/L; Table 1)[6,9] and ganglionic acetylcholine receptor (AChR) antibody (0.08 nmol/L; normal range, ≤0.02 nmol/L).[4] Because these antibodies may be associated with malignancy (most common are lung carcinoma, thymoma, ovarian, or breast carcinoma;[5–9] however, we have not yet encountered a voltage-gated calcium-channel antibody with thymoma[7]), we performed a computerized tomography scan of the chest, abdomen, and pelvis, a mammogram, and a dermatologic examination. All were negative. Radioimmunoprecipitation assays for other cation channel antibodies (muscle AChR, neuronal voltage-gated P/Q-type calcium channel, and potassium channel) and glutamic acid decarboxylase-65 antibody, enzyme-linked immunosorbent assay (for muscle-striated antibody), indirect immunofluorescence, and Western blot assays (for neuronal cytoplasmic and nuclear autoantibodies) all were negative.

The detection of 2 neuronal autoantibodies that are common accompaniments of autoimmune dysautonomia[4–8] prompted the performance of an autonomic reflex study, which revealed mild, patchy, autonomic dysfunction with evidence of mild sudomotor dysfunction. Because a detailed evaluation for cancer was negative, the diagnosis of idiopathic AGID was made as the basis for the patient's gastroparesis.

The presence of ganglionic AChR antibody prompted a trial of pyridostigmine in an attempt to enhance cholinergic synaptic transmission in the autonomic and enteric nervous systems. Oral pyridostigmine was initiated at 30 mg, twice a day, for 4 days and advanced to 30 mg, 3 times a day. The patient reported significant improvement in GI symptoms with stabilization of weight within 1 month. Maintenance of low-dose pyridostigmine (30 mg, 3 times a day), supplemented by tegaserod (3 mg at bedtime), sustained the improvement in GI symptoms without side effects, except for mild subjective dizziness after intake of the pyridostigmine.

Discussion

Healthy GI motility is orchestrated by coordination of extrinsic (parasympathetic and sympathetic) and intrinsic (enteric) neural pathways, neuroendocrine circuitry, and smooth muscle excitability, which is influenced by interstitial cells of Cajal. GI dysmotility results from perturbation in any of these interacting systems. Animal studies have shown that viruses and other pathogenic agents may damage the enteric nervous system, either directly or by immune-mediated mechanisms,[10] and that autoimmunity directed at autonomic and enteric ganglionic neurons is a cause of AGID[11,12] as a limited manifestation of autoimmune autonomic neuropathy (AAN). Clinically, AAN is an acquired disorder that can present subacutely (peak autonomic dysfunction in 3 months) or as a chronic condition (peak autonomic dysfunction after 3 months).[4,13] It encompasses both paraneoplastic and idiopathic disorders, and an antecedent event frequently is reported, such as a viral illness, trauma, or general anesthesia.[14]

The autoimmune response that causes AAN is reflected by a profile of circulating neuronal and muscle antibodies. Ganglionic AChR antibodies targeting nicotinic AChRs in both autonomic and enteric ganglia are detectable in 50% of patients with idiopathic AAN.[4,13] Although this antibody is useful diagnos-

Table 1. Serum Autoantibody Profile (Paraneoplastic Antibody Evaluation)

Autoantibody specificity	Value	Normal range	Units
Calcium channel, N-type	0.09[a]	0.00–0.02	nmol/L
Calcium channel, P/Q-type	0.00	0.00–0.02	nmol/L
CRMP-5, Western blot	Negative	Negative	—
Ganglionic AChR	0.08[a]	0.00–0.02	nmol/L
Muscle AChR	0.00	0.00–0.02	nmol/L
Striated muscle	<1:60	<1:60	Serum dilution
Glutamic acid decarboxylase-65	0.00	00–0.02	nmol/L
Purkinje cell cytoplasmic, type 1	<1:120	<1:120	Serum dilution
Purkinje cell cytoplasmic, type 2	<1:120	<1:120	Serum dilution
Purkinje cell cytoplasmic, type Tr	<1:120	<1:120	Serum dilution
ANNA-1	<1:120	<120	Serum dilution
ANNA-2	<1:120	<120	Serum dilution
ANNA-3	<1:120	<120	Serum dilution

[a]Positive values.

tically as a serologic marker, its absence does not exclude the diagnosis of AAN. We estimate that less than 50% of patients with ganglionic AChR antibody have an underlying malignancy (VA Lennon; unpublished observation). To date, autoantibodies of ganglionic AChR specificity are the only proven effectors of autonomic dysfunction, including GI dysmotility. When injected into naive mice, antibodies isolated from sera of immunized rabbits or patients transfer signs of AAN.[12] GI dysmotility is the most prominent sign of experimentally induced AAN. Serum levels of ganglionic AChR antibody correlate with the clinical severity of AAN, both in patients[4] and in laboratory animals immunized with ganglionic AChR protein,[11] and clinical improvement in autonomic symptoms is paralleled by a decrease in serum levels of ganglionic AChR antibody.[4,12] Animals immunized with ganglionic AChR protein do not show pathologic evidence of enteric ganglionitis (VA Lennon, unpublished observation). Additional molecular targets implicated in the pathogenesis of AGID include the Hu family of RNA binding proteins,[2] neuronal N-type calcium channel,[5,8] smooth muscle L-type calcium channel,[15] the collapsin response-mediator protein-5 (CRMP-5), and the Purkinje cell cytoplasmic protein Yo[8] (which also is expressed in enteric and autonomic ganglia[16]). The antibodies associated most commonly with paraneoplastic dysmotility include ANNA-1 (anti-Hu) and N-type calcium-channel antibodies,[1,2,6,8] but neoplasm is not always found.[17] A comprehensive serologic evaluation is required to establish the likelihood of an underlying malignancy.[5]

The patient of this report had AGID as an idiopathic and limited form of AAN, for which neuronal autoantibodies specific for ganglionic AChR and N-type calcium channels served as biomarkers. The spectrum of AGID includes esophageal achalasia, gastroparesis (with intractable emesis, early satiety, and postprandial pain), pseudohypertrophic pyloric obstruction, intestinal pseudo-obstruction, megacolon (slow transit), and anal spasm.[18] In our experience to date, mild localized forms of AGID are less likely to be inflammatory than those associated with neuronal nuclear or cytoplasmic autoantibodies (ANNA-1 and CRMP-5-IgG) as exemplified by paraneoplastic cases. The ready reversibility of this patient's GI symptoms by acetylcholinesterase inhibition, despite a 15-year history, supports an immunopharmacologic rather than structural lesion.[19] Enteric ganglionitis involves progressive degeneration and loss of enteric neurons,[1] and cytotoxic T cells are implicated pathogenically.[2,5] The rationale for the trial of acetylcholinesterase inhibitor in this patient was by analogy with the first line of treatment for myasthenia gravis,[19] and because of the remarkable effect on colonic motility observed in a previous patient (patient 3; also ganglionic AChR antibody-positive[20]) who was given neostigmine methyl sulfate intravenously in the course of GI imaging for an atonic colon that lacked response to meals.

Management of AGID includes symptom relief, search for underlying neoplasm (with long-term surveillance if strongly predictive marker autoantibodies are detected, such as anti-neuronal nuclear autoantibody-type 1 (also known as "anti-Hu" [ANNA-1]); CRMP-5-IgG, or Purkinje cell cytoplasmic autoantibody-type 1 (also known as "anti-Yo" [PCA-1][8]), definitive treatment of the neoplasm, immunomodulatory therapy, and supportive treatment. Maintenance of nutrition and hydration, treatment of small-bowel bacterial overgrowth, and management of abdominal pain are important supportive measures. A dramatic clinical response sometimes follows administration of acetylcholinesterase inhibitor (pyridostigmine), intravenous immune globulin, or plasmapheresis.[21] Long-term management may require immunosuppressive medication, such as adrenocorticosteroids and azathioprine or cyclophosphamide. Our patient's remarkably long history influenced our decision not to initiate immunosuppressant therapy.

This patient's presentation with symptoms of severe gastroparesis, without an obvious underlying cause, and minimal clinical response to promotility agents prompted autoimmune serologic evaluation, which revealed N-type calcium-channel and ganglionic AChR antibodies. The diagnosis of AGID was made, and an underlying malignancy was excluded. Treatment with pyridostigmine led to resolution of the GI symptoms and stabilization of weight. The diagnosis of a limited form of AAN should be considered in all adult patients with unexplained gastroparesis. In view of this drug's comparative safety, a trial of oral pyridostigmine is justifiable even in seronegative patients. Malignancy should be excluded, especially in patients older than 50 years, or with a history of tobacco use or asbestos exposure. Gastrointestinal dysmotility also is a common accompaniment of diabetes. Although type-2 diabetes is estimated (on clinical grounds) to be the form associated more commonly with GI dysmotility, one might predict that AGID would occur more frequently with type-1 diabetes which, similar to AGID, is an organ-specific autoimmune disorder. Indirect experimental data suggest that some type-1 diabetic patients' sera contain IgG that selectively disrupts intestinal motility by activating an L-type calcium channel in gut smooth muscle.[15] Our patient had normal fasting plasma glucose and was seronegative for glutamic acid decarboxylase-65 antibody (the most common autoantibody marker of type-1 diabetes, and a frequent accompaniment of thymoma[7]). AGID remains an underrecognized cause of GI dysmotility. Its diagnosis and management rely on new diagnostic and therapeutic strategies introduced by advances in autoimmune neurology.

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