60-Year-Old Man With Chronic Diarrhea and Peptic Ulcer Disease

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A 60-year-old man was transferred to our hospital with a 5-year history of worsening daily watery, nonbloody, nongreasy diarrhea. One year previously, recurrent vomiting had developed. Over the month preceding the current admission, he experienced 4 episodes of intractable, large-volume diarrhea with abdominal pain, upper and lower extremity muscle cramping, and orthostatic light-headedness. His diarrhea did not improve with fasting, and each of these episodes required hospitalization for intravenous fluid and electrolyte replacement. On the fourth episode, he was transferred to our institution for further diagnostic evaluation.

The patient reported no symptomatic correlation to dietary habits and no associated fever, gastrointestinal bleeding, flushing, arthralgia, or rash. He had not experienced fecal incontinence. His medical history was notable for gastroesophageal reflux disease diagnosed 4 years previously and treated with 40 mg of esomeprazole daily. He had no surgical history. His only other medication was lisinopril for hypertension, and he reported no recent medication changes or antibiotic therapy. His family history did not include any gastrointestinal illness or malignant neoplasms, and he did not use tobacco or alcohol. His last screening colonoscopy was within the past 5 years and yielded normal findings.

The patient had been stabilized with intravenous fluids before arrival at our institution, and physical examination at presentation revealed a well-nourished man with a body mass index of 26.3 kg/m^2, normal orthostatic vital signs, and normal physical examination findings, including no evidence of rash, abdominal tenderness, fecal impaction, or other abnormality.

The results of laboratory studies including red and white blood cell count, complete metabolic profile, calcium level, liver function tests, total protein, albumin, thyrotropin, and tissue transglutaminase antibody values, erythrocyte sedimentation rate, and C-reactive protein concentration were all within normal limits. Stool studies were negative for blood, fecal fat, leukocytes, enteric pathogens, ova and parasites, and *Clostridium difficile*. A review of recent laboratory values obtained during previous hospitalizations revealed the following remarkable findings (reference ranges shown parenthetically): magnesium, 0.0 mg/dL (1.7-2.3 mg/dL), confirmed on repeated laboratory testing, and potassium, 2.9 mmol/L (3.6-5.2 mmol/L). A quantification of an episode of diarrhea revealed 1.2 L of watery stool. Studies of stool electrolytes yielded a stool sodium concentration of 70 mmol/L and a stool potassium concentration of 60 mmol/L.

1. Which *one* of the following is the *most likely* etiology of this patient's chronic diarrhea?

a. Osmotic
b. Secretory
c. Infectious
d. Factitious
e. Malabsorptive

The stool osmotic gap is a useful measure to help classify chronic diarrhea as osmotic or secretory. Neither the small bowel nor the colon is able to maintain an osmotic gradient, and therefore, unabsorbed or secreted ions obligate retention of water to maintain the osmolality of stool similar to that of plasma at 290 mOsm/kg. In osmotic diarrhea, a nonabsorbable ingested solute is the driver for water retention in the intestinal lumen, whereas in secretory diarrhea, water retention is attributed to secreted (chloride or bicarbonate) or incompletely absorbed (sodium) electrolytes. By applying these concepts, a calculation can be made to detect an osmotic gap resulting from ingestion of a poorly absorbed substance. Because measured stool osmolality is subject to changes because of continued bacterial metabolism after stool collection, it is usually not a reliable test, and calculations should be made from an expected fecal osmolality of 290 mOsm/kg^2.

See end of article for correct answers to questions.

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The stool osmotic gap is calculated with the formula $290 - 2([Na^+] + [K^+])$ where the sum of stool sodium and potassium concentrations are doubled and subtracted from 290. In the setting of chronic diarrhea, a small gap (<50 mOsm/kg) is suggestive of a secretory diarrhea. When the osmotic gap is large (>100 mOsm/kg), an unaccounted ion is present and suggests an osmotic diarrhea.[1] In our patient, the calculated stool osmotic gap is $290 - 2 \times (70 + 60) = 30$, which suggests a secretory diarrhea. Additionally, symptoms that do not improve with fasting and large-volume watery stools are associated with secretory diarrhea.[2]

Infections are the most common of cause of secretory diarrhea; however, chronic persistent infectious diarrhea is rare in immunocompetent individuals. Commonly, bacterial diarrhea presents as an acute illness, but it would be unlikely in the absence of fecal enteric pathogens, leukocytes, ova and parasites, and *C difficile*. Yeast and fungi, mainly *Candida albicans*, and Whipple disease may be chronic infectious etiologies but are less common.[2]

Factitious diarrhea is associated with laxative abuse or intentional dilution of stool specimens. A large stool osmotic gap may be present if laxatives contain magnesium, but the osmotic gap may be normal with phosphate- or sulfate-based laxatives. The presence of melanosis coli on colonoscopy should raise the concern for laxative use. A low measured stool osmolality is associated with dilution of stool specimens. A high index of suspicion is necessary, especially for patients with known psychiatric or eating disorders or association with health care professions.[3,4] Other more likely causes of chronic diarrhea first need to be excluded.

Malabsorptive diarrhea, also a form of osmotic diarrhea, has a broad differential that includes mucosal or structural disease and pancreatic insufficiency leading to carbohydrate and/or fat malabsorption. Important clinical features include a history of bowel resection, symptoms of weight loss, steatorrhea, muscle wasting, vitamin deficiencies, and failure to thrive.[4] Given the lack of weight loss, negative results on celiac disease serology, normal fecal fat level, and low stool osmotic gap, a malabsorptive diarrhea is not the most likely cause of this patient's diarrhea.

As calculated by the stool osmotic gap, this patient's chronic diarrhea was attributed to a secretory cause. The patient continued to have watery diarrhea during his hospitalization, and intravenous fluids were given for volume replacement. He continued to have hypokalemia and hypomagnesemia and required continued electrolyte replacement.

2. In view of the findings thus far, which *one* of the following is the *best* test to evaluate this patient's chronic diarrhea?

a. Small bowel follow-through radiographic study
b. Abdominal computed tomography (CT)
c. CT enterography
d. Colonoscopy
e. Sigmoidoscopy and esophagogastroduodenoscopy (EGD)

A small bowel follow-through radiographic study uses barium contrast medium and can highlight structural abnormalities in the stomach, esophagus, and small bowel. Computed tomography further visualizes soft tissue and can be helpful for detecting masses in the liver, pancreas, or intestines. Computed tomographic enterography uses contrast medium to enhance the bowel wall and can help diagnose inflammatory bowel disease and neoplasms and detect more subtle mural findings.

Because the patient is up-to-date with screening colonoscopy, sigmoidoscopy is preferred over colonoscopy because it has the advantages of simpler preparation, no need for sedation, and lower associated risk. If more proximal disease, such as Crohn disease, is suspected, a full colonoscopy should be performed.[2] Our patient does not have elevated inflammatory markers, bloody diarrhea, or weight loss to suggest inflammatory bowel disease, and an initial sigmoidoscopy is sufficient. Because the patient also presented with symptoms of nausea and vomiting, EGD is appropriate to rule out small bowel disease that can present with large volumes of diarrhea (>1 L/d).[2]

The patient underwent sigmoidoscopy, which did not reveal any remarkable gross or microscopic findings. Esophagogastroduodenoscopy revealed numerous ulcerations in and beyond the second portion of the duodenum. Because of the EGD findings, CT enterography was performed, which detected a 7-mm hypervascular nodule in the duodenal

Mayo Clin Proc. ■ January 2015;90(1):e1-e5 ■ http://dx.doi.org/10.1016/j.mayocp.2014.05.022
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wall. There was no evidence of pancreatic, hepatic, or intestinal masses.

3. Which *one* of the following would be the *best* test to confirm the diagnosis at this time?

a. Magnetic resonance imaging (MRI) of the abdomen
b. Positron emission tomography (PET)/CT
c. Indium 111 (^{111}In) octreotide single-photon emission CT (SPECT)
d. Secretin stimulation test
e. Serum gastrin measurement

In the setting of this patient's chronic secretory diarrhea, a mass in the duodenal wall is concerning for a neuroendocrine tumor (NET). Although extremely rare, it should be suspected when factitious and other organic causes of chronic diarrhea have been excluded. Secretory diarrhea caused by peptide hormones such as gastrin or vasoactive intestinal polypeptide (VIP) can be associated with large-volume (>1 L/d) diarrhea, volume depletion, and substantial electrolyte abnormalities.[2]

All of the options would be appropriate in evaluating for NETs because a multimodal approach is recommended.[5] Magnetic resonance imaging and PET/CT can be helpful in localizing and characterizing tumors, especially when initial CT or endoscopic findings are inconclusive.[5] However, ^{111}In octreotide SPECT would be the best test to confirm the diagnosis, and the other studies can be considered if ^{111}In octreotide SPECT is unavailable or the results are inconclusive. Imaging with radiolabeled octreotide has a sensitivity of 75% to detect VIP-secreting tumors, glucagonomas, and gastrinomas because of the overexpression of somatostatin receptor in functional NETs. A positive study result will confirm that the mural mass seen in this patient is a functionally active NET and will explain his symptoms and guide next steps in management.

A secretin stimulation test should be performed in patients with suspected gastrinoma who have nondiagnostic gastrin laboratory test results,[6] but this test must be performed after discontinuation of proton pump inhibitors (PPIs) for at least 2 weeks to avoid false-positive results.[7] Like the secretin stimulation test, fasting gastrin levels should not be measured until the patient has discontinued PPI therapy for at least 2 weeks because 20% to 30% of patients receiving long-term PPI therapy can have gastrin levels as high as 5 times the normal value, a level seen in nearly 60% of patients with gastrinoma.[8] In addition to PPI therapy, other conditions that cause hypochlorhydria include atrophic gastritis, pernicious anemia, and gastric cancer. Elevated gastrin levels with hyperchlorhydria are associated with *Helicobacter pylori* infection, G-cell hyperfunction or hyperplasia, and Zollinger-Ellison syndrome (ZES).[8]

Because our patient's volume depletion was so severe that he required hospitalization, a 2-week cessation of PPI therapy and reevaluation with serum testing was not feasible. He underwent ^{111}In octreotide SPECT, which confirmed that the duodenal wall nodule detected on CT enterography was functionally active. There was no evidence of any other site of enhancement or activity. Serum VIP levels were measured and found to be normal. A fasting gastrin test was nevertheless obtained while PPI therapy was continued, and the results were inconclusive at 5 times the upper limit of normal.

With the patient's EGD revealing numerous ulcerations characteristically in the distal duodenum and the positive ^{111}In octreotide SPECT results, a clinical diagnosis of gastrinoma was made and discussed with the patient. He wished to pursue immediate treatment for the gastrinoma.

4. Which *one* of the following is the *best* overall treatment option for this patient?

a. Long-term high-dose PPI therapy
b. Somatostatin analogue therapy
c. Chemotherapy
d. Exploratory laparotomy
e. External beam radiotherapy

This patient has ZES, which is characterized by gastrinoma with severe peptic ulcer disease. First-line treatment for ZES includes high-dose PPI therapy for symptomatic treatment. Somatostatin analogues have not been as successful and are reserved for refractory cases. There is insufficient data to indicate the use of chemotherapy for ZES treatment.[5] Evaluation for metastatic disease is important to guide treatment because patients with hepatic metastasis are not candidates for surgery and should be managed symptomatically. Patients

with nonmetastatic lesions, even if not initially visualized, should undergo exploratory laparotomy with intent for surgical resection.[5,9] The current role of external beam radiotherapy is unclear, although it may be used for palliative treatment.[5]

The patient had no evidence of metastasis on previous CT and was referred to the hospital neuroendocrine surgery team. He was treated with high-dose (40 mg twice daily) esomeprazole until he underwent exploratory laparotomy with duodenotomy and excision of a submucosal tumor. Pathologic examination revealed a 9×8×5-mm well-differentiated neuroendocrine neoplasm. The patient's symptoms resolved abruptly after surgery.

5. Which *one* of the following statements is *true* about the patient's condition?

a. The condition is usually very aggressive with a short clinical course
b. Surgical resection of lesions without hepatic metastasis is associated with high cure rates
c. Hepatic metastasis is more common in multiple endocrine neoplasia type I (MEN-I)
d. Duodenal primary lesions have a worse prognosis than pancreatic primary lesions
e. Mortality with lymph node metastasis is comparable to that of hepatic metastasis

Gastrinomas are typically not aggressive and are slow growing, as seen in this patient's protracted clinical course. Gastrinomas have been classified as benign or malignant, with malignancy associated mainly with hepatic metastasis. MEN-1—associated gastrinoma less frequently presents with hepatic metastasis and portends a better postresection prognosis. Pancreatic primary lesions have a worse prognosis than duodenal lesions and are larger at the time of detection. Postresection survival for patients with lymph node metastasis is no worse than that for those with only primary lesions. It is therefore true that surgical resection of gastrinoma without hepatic metastasis has a good prognosis, and cure rates are high with 83% survival at 15 years. As a comparison, patients with liver metastasis have a 10-year survival of only 30%.[9]

Three years after surgical resection, the patient continues to do well. His diarrhea has resolved, and follow-up of duodenal ulcerations by EGD revealed complete healing postresection. He has had no evidence of recurrence of gastrinoma at follow-up evaluation.

DISCUSSION

Zollinger-Ellison syndrome is an extremely rare cause of chronic secretory diarrhea and peptic ulcer disease caused by acid hypersecretion secondary to gastrinoma. It is estimated that the annual incidence is less than 1 in 1,000,000 per year.[4] It can present clinically with peptic ulcer disease with multiple ulcerations seen beyond the second portion of the duodenum on EGD and can be associated with large-volume watery diarrhea, volume depletion, and electrolyte derangement.[2,4]

An algorithmic approach to chronic diarrhea should be based on history and clinical findings to first exclude more common causes.[2,4] Tools such as the stool anion gap can help determine osmotic and secretory types of chronic diarrhea.[1,3] When a neuroendocrine secretory diarrhea is suspected, a multimodal evaluation should be pursued with measurement of neuroendocrine peptide levels including fasting gastrin, VIP, urinary 5-hydroxyindoleacetic acid, and chromogranin A.[10] Gastrin, secretin, and chromogranin A, a nonspecific marker for NETs, can be substantially elevated in individuals taking PPIs, and these medications should be discontinued at least 2 weeks before testing.[8] Secretin stimulation testing can confirm gastrinoma when gastrin levels are inconclusive, and imaging modalities including CT, PET/CT, MRI, endoscopic ultrasonography, and ^{111}In octreotide SPECT can help localize a lesion.[5,6]

Because of high surgical cure rates, patients with suspected gastrinoma, including those without a localized lesion, should undergo exploratory laparotomy.[5] Hepatic, but not lymph node, metastasis precludes surgical treatment and portends a poor prognosis with high 5- to 10-year mortality. Primary tumors located in the duodenum rather than the pancreas and those associated with MEN-1 (20%) portend the best postresection survival. Overall survival after resection in all gastrinomas without hepatic metastasis is excellent.[9] In nonsurgical candidates with ZES, symptomatic management with high-dose PPI therapy should be pursued. The role of other therapies such as chemotherapy and radiation for the treatment of ZES are still under investigation.[5]

Mayo Clin Proc. ■ January 2015;90(1):e1-e5 ■ http://dx.doi.org/10.1016/j.mayocp.2014.05.022
www.mayoclinicproceedings.org

The National Comprehensive Cancer Network recommends that patients undergo surveillance at 3 months postresection with history, physical examination, and repeated CT or MRI. Semiannual or annual follow-up should be maintained thereafter for up to 10 years, with consideration of continued chromogranin A and gastrin monitoring and repeated imaging as clinically indicated.[10]

This case illustrates that although chronic diarrhea is common, a methodical and thorough approach is important to not overlook rare but potentially serious, yet curable, conditions such as ZES.

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CORRECT ANSWERS: 1. b. 2. e. 3. c. 4. d. 5. b