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A SELF-TEST ON A CLINICAL CASE

A 48-year-old woman with nausea, vomiting, early satiety, and weight loss

A 48-YEAR-OLD female ice-skating teacher is seen for evaluation of progressive gastrointestinal (GI) symptoms. For 6 to 7 years, she has had intermittent pain in the upper and middle abdomen. The pain is dull, nonradiating, and worse after eating. She underwent cholecystectomy about 5 years ago because of this pain, but it did not provide much relief.

About a year and a half ago, she started to experience nausea, vomiting, early satiety, and postprandial abdominal bloating. Over this period, she developed anorexia, particularly for fatty foods, and she has lost 20 pounds. She is also having intermittent loose stools. Her pain, however, has not changed in character or severity.

She has no significant past medical history. She had an appendectomy 10 years ago and a partial thyroidectomy for a benign nodule. Her only medication is prochlorperazine, which she takes as needed for nausea and vomiting.

She has smoked one pack of cigarettes per day for 25 years and denies alcohol intake. Her maternal grandfather and granduncle died of colon cancer. There is no family history of inflammatory bowel disease. Review of other systems is unremarkable.

Physical examination

The patient appears thin but in no distress. Her blood pressure is 114/65 mm Hg with no orthostasis, pulse 68/minute, height 5'5", and weight 102.9 pounds. Her heart and lungs are normal.

This paper discusses therapies that are experimental or are not approved by the US Food and Drug Administration for the use under discussion.

Her abdomen has scars from her cholecystectomy and appendectomy incisions. There is no distension, tenderness, or organomegaly. A bruit is audible in the upper abdomen; she has no carotid or femoral bruits.

Laboratory data

Her chemistry panel, complete blood count, erythrocyte sedimentation rate, and C-reactive protein level are normal, except for low concentrations of protein (4.1 g/dL, normal 6.0–8.4), albumin (2.4 g/dL, normal 4.0–5.4), and thyroid-stimulating hormone (0.25 µU/mL, normal 0.4–5.5).

The patient has lost 20 pounds in 1 1/2 years

DIFFERENTIAL DIAGNOSIS

1 Which of the following is the least likely diagnosis?

- ❑ Peptic ulcer disease
- ❑ Chronic pancreatitis
- ❑ Irritable bowel syndrome
- ❑ Gastroparesis

Peptic ulcers are most commonly caused by either *Helicobacter pylori* (about 70% of duodenal ulcers and 50% to 60% of gastric ulcers[1]) or nonsteroidal anti-inflammatory drugs. The common presenting symptoms include dyspepsia and abdominal pain, but most ulcers may be asymptomatic.[2]

In about 10% of cases, chronic gastroduodenal ulcers can result in gastric outlet obstruction due to fibrosis and scarring.[3] The onset of obstruction is heralded by nausea, vomiting, postprandial abdominal bloating, pain, and weight loss.

Chronic pancreatitis is characterized by abdominal pain that radiates to the back and,

in advanced cases, by pancreatic insufficiency. The pain may be continuous but worse after eating. Patients intentionally eat less to avoid the pain, which leads to severe weight loss.[4] Steatorrhea occurs when lipase secretion has diminished by 90%.[5] Significant nausea and vomiting are not commonly observed in chronic pancreatitis.

Gastroparesis causes symptoms of gastric outlet obstruction, including nausea, vomiting, abdominal bloating, early satiety, and weight loss[6] and should be considered in the differential diagnosis when these symptoms are present, particularly in women in their 40s and 50s.

Irritable bowel syndrome is the least likely diagnosis. The Rome II criteria[7] for this diagnosis require that the patient have experienced abdominal pain or discomfort for at least 12 weeks (not necessarily consecutive) in the past 12 months, and that the pain have at least two of the three following features:

- It is relieved by defecation
- Its onset is associated with a change in frequency of stool
- Its onset is associated with a change in form (appearance) of stool.

Certain "alarm features" preclude the diagnosis of irritable bowel syndrome and warrant appropriate investigation: gastrointestinal bleeding, weight loss greater than 10 pounds, a family history of colon cancer, recurring fever, anemia, and chronic severe diarrhea or constipation.

Our patient does not meet the Rome II criteria, owing to her unintentional weight loss. In addition, her abdominal bruit is worrisome and suggests another diagnosis.

Gastroparesis should be considered especially in women in their 40s and 50s with appropriate symptoms

DIAGNOSTIC WORKUP

2 Which of the following would be the most appropriate first step in this patient's diagnostic workup?

- ❑ Esophagogastroduodenoscopy (EGD; upper GI endoscopy)
- ❑ Dietary restriction and anticholinergic agents
- ❑ Computed tomography (CT) of the abdomen
- ❑ Solid-phase gastric emptying test

EGD should be the first investigation in any patient who presents with symptoms of gastric outlet obstruction, as it can rule out mechanical causes such as scarring and fibrosis of the pylorus due to peptic ulcers and gastric antral neoplasia.

Duodenal obstruction is uncommon and is most often due to extrinsic causes such as compression from a pancreatic tumor or surrounding lymph node metastases. A rare cause of duodenal obstruction is the superior mesenteric artery (SMA) syndrome, in which the third part of the duodenum is trapped between a "calcified" or "acute-angled" SMA and the aorta or spine. Its clinical significance is controversial, its symptoms are nonspecific, and it is difficult to diagnose.

Upper gastrointestinal radiographic studies with contrast should be avoided in patients with suspected gastric outlet obstruction because the barium contrast in the stomach makes it impossible to examine the mucosa properly if an endoscopic study is performed soon afterward, until the barium is passed or removed by nasogastric suction. Furthermore, endoscopy is more sensitive for detecting mucosal lesions[8] and allows biopsy of lesions if required. On the other hand, a series of upper gastrointestinal radiographs may provide anatomical delineation if endoscopy is contraindicated or difficult owing to a tight stricture.

Dietary restriction and anticholinergic agents are treatments for irritable bowel syndrome and have no role here.

CT of the abdomen is useful in evaluating upper abdominal symptoms and gives information about the pancreas, liver, gallbladder, common bile duct, and retroperitoneum.

A solid-phase gastric emptying test is warranted if no mechanical obstruction is found on EGD in a patient with symptoms of gastric outlet obstruction.

Case continued

The patient had undergone an extensive evaluation at another hospital.

- Thyroid function tests, the 72-hour fecal fat content, the serum gastrin level, and catecholamine levels were all normal.
- An upper GI endoscopic study showed a large amount of food residue in the stomach with chronic nonerosive gastritis but was otherwise normal.

TABLE 1

- A CT scan of the abdomen showed that the stomach was dilated and filled with fluid and debris and the small bowel was diffusely dilated without a transition point. The liver, pancreas, and spleen were normal.
- On solid-phase gastric emptying testing, the half-life of stomach emptying was 454 minutes (normal 60–90).
- A series of small bowel radiographs showed markedly delayed transit time to the colon. The small bowel mucosa had a normal pattern.

These findings—the delayed solid-phase gastric emptying, the dilated and residue-filled stomach on EGD and CT, as well as the markedly dilated stomach—confirmed the diagnosis of gastroparesis. Subsequently, antroduodenal motility studies were done to rule out chronic intestinal pseudo-obstruction, and these studies were normal. Even after exhaustive investigations, no etiologic factor could be identified, and the patient's gastroparesis was deemed idiopathic.

GASTROPARESIS

Gastroparesis is a motility disorder of the stomach characterized by symptoms of gastric outlet obstruction in the absence of mechanical causes.

Gastric motility is modulated by gastric myoelectrical activity, a part of a local neural network. It is also regulated by meal composition and hormonal mechanisms.[9] Fatty meals delay emptying, as do secretin and cholecystokinin, whereas motilin and neurotensin accelerate it. Neurologic mechanisms include parasympathetic (vagal) and sympathetic influences along with gastrointestinal reflexes.

Soykan et al[6] reported a series of 146 patients with gastroparesis. The most common symptoms were nausea (present in 92%), vomiting (84%), abdominal bloating (75%), early satiety (60%), and abdominal pain (46%). In a series of 28 patients, Hoogerwerf et al[10] reported abdominal pain in 90%, early satiety in 86%, and vomiting in 68%. Occasionally, an audible and palpable succussion splash may be noticed.

Women are more likely than men to have impaired gastric emptying, particularly during the luteal phase of the menstrual cycle.[11] In the series reported by Soykan et al,[6] women constituted 82% of all patients. The mean age was 45 years and the mean age at symptom onset was 33.7 years.

In almost 80% of the cases in these series, the cause of gastroparesis was either idiopathic, diabetes mellitus, or prior gastric surgery (TABLE 1). Another 15% were due to Parkinson

TABLE 2

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disease, a connective tissue disorder, or chronic intestinal pseudo-obstruction. Idiopathic gastroparesis occurs almost exclusively in women, about 90% in these series.

Evaluation of gastroparesis

A high index of suspicion is required to make the diagnosis of gastroparesis. A detailed history and physical examination should be the first step in evaluating patients with suspected gastroparesis (TABLE 2). Next, EGD should be done to rule out mechanical causes of gastric outlet obstruction.

The solid-phase gastric emptying test is the gold standard to confirm the diagnosis. Traditionally, the patient fasts overnight and then eats a meal of eggs that contains 1 millicurie of technetium-99 sulfur colloid. A scintigraphy camera measures radioactivity over the stomach at 0, 60, and 90 minutes, and a graph is plotted to determine the emptying time. The time for the radioactivity to diminish to 50% is normally 60 to 90 minutes.[12] Extending scintigraphy to 4 hours increases the detection of delayed gastric emptying.[12]

However, a newer standard has been established, based on a multicenter study in 123 normal volunteers.[13] In the new protocol, the patient consumes a technetium-99-labeled low-fat meal (egg substitute), and the percent intragastric residual content is measured at 60, 120, and 240 minutes. The median and 95th percentile values are as follows:

- 60 minutes: median 69%, 95th percentile 90%
- 120 minutes: median 24%, 95th percentile 60%
- 240 minutes: median 1.2%, 95th percentile 10%.

Gastric emptying is considered delayed if the residual content is more than 10% at 4 hours.

Gastric emptying is considered delayed if > 10% remains at 4 hours

Searching for a cause of gastroparesis

Once a diagnosis of gastroparesis is confirmed, etiologic factors must be sought (TABLE 1).

Diagnostic tests (not widely available) include breath tests, electrogastrography, and antroduodenal manometry. Breath tests for gastric emptying using carbon-13-labeled octanoate, a medium-chain triglyceride, have been used in clinical trials and pharmaceutical research, but not often in clinical practice. They are an indirect measure of gastric emptying that can be used as an office-based procedure.[14]

Electrogastrography is the recording of gastric myoelectrical activity using cutaneous electrodes placed on the anterior abdominal wall. Gastric dysrhythmias (tachygastria and bradygastria) and decreased postprandial amplitude have been described in idiopathic and diabetic gastroparesis.[15] Studies have demonstrated a good correlation between delayed gastric emptying by scintigraphy and abnormal findings on electrogastrography.[15]

TABLE 3

Prokinetic agents used in gastroparesis

DRUG	MECHANISM	MAIN EFFECTS	DOSAGE*	SIDE EFFECTS	MAXIMUM EFFECT†
Metoclopramide‡	Dopamine antagonist	Prokinetic, antiemetic	5–20 mg four times a day by mouth, intravenously, subcutaneously, per rectum, or intraperitoneally	Dystonia, parkinsonism	4–12 weeks
Domperidone§	Dopamine antagonist	Prokinetic, antiemetic	10–20 mg four times a day by mouth	Breast engorgement, galactorrhea	4–12 weeks
Erythromycin‖	Motilin agonist	Prokinetic	125–250 mg four times a day by mouth or 250 mg every 8 hours intravenously	Nausea, abdominal pain	4 weeks
Cisapride§	5-HT4 receptor agonist	Prokinetic	10–20 mg four times a day by mouth	Prolonged QT	1 year
Tegaserod	5-HT4 receptor partial agonist	Prokinetic	6 mg three times a day or 12 mg twice a day by mouth	Diarrhea, abdominal pain	Weeks

*Elixirs are preferable to tablets and capsules
†Time until maximum effect is seen
‡Approved by the US Food and Drug Administration for this indication
§Available only through special protocols
‖Also used in acute gastroparesis, particularly during the postoperative period

Antroduodenal manometry provides information about the coordination of gastric and duodenal motor function in both the fasting and the postprandial periods. It is mainly used to determine neuropathic or myopathic disorders and chronic intestinal pseudo-obstruction.[16] In a myopathic process the amplitude of contractions is diminished; in contrast, in a neuropathic process the coordination is disorganized.

TREATMENT

3 Which of the following is not a known treatment for gastroparesis?

- ❑ Low-fat diet
- ❑ Tight glucose control
- ❑ Antiemetic agents
- ❑ Prokinetic agents
- ❑ Botulinum toxin
- ❑ Gastric electrical pacing
- ❑ Gastric tube feedings

The general principles of treatment of gastroparesis are to correct fluid, electrolyte, and nutritional imbalances; to identify and treat the underlying cause; and if the cause is not correctable, then to control the symptoms.

Gastric tube feedings are not a treatment for gastroparesis and generally are not offered to patients with this condition. There is no evidence to suggest that they either exacerbate or alleviate symptoms in mild to moderate gastroparesis.

Gastrostomy tubes to vent the stomach have, however, been shown to relieve symptoms of nausea and emesis in refractory gastroparesis, and jejunal tube feedings have been shown to be effective in reducing morbidity and improving quality of life in patients with severe refractory gastroparesis.[17] Often, a

percutaneous gastrostomy tube for venting and a percutaneous jejunostomy tube for feeding work better in combination than alone.[18]

Low-fat diet. As liquid emptying is usually normal in gastroparesis, liquid nutrition should be encouraged. Fats delay gastric emptying by promoting the release of inhibitory cholecystokinin, and low-fat, high-carbohydrate meals are therefore recommended. Frequent, small, low-residue meals are preferable.

Tight glucose control. In people with diabetes, optimum glucose control can improve gastric myoelectrical activity,[19] whereas glucose levels above 150 mg/dL can impede gastric emptying.[20]

Antiemetic agents

Antiemetic agents are the most widely used drugs for gastroparesis, since nausea and vomiting are the most common symptoms and also due to the relative ineffectiveness of other drug classes. The important classes are the phenothiazines, antihistamines, and antagonists of the serotonin 5-HT3 receptor. As a general rule, medications used in gastroparesis should not be considered ineffective until full therapeutic dosages have been used.

Fatty foods delay gastric emptying and should be avoided in patients with gastroparesis

Phenothiazines include prochlorperazine, trimethobenzamide, and promethazine. Elixirs and suppositories are preferable to other preparations. Long-term use is generally safe, but sedation and extrapyramidal symptoms are the important side effects.

Antihistamines include diphenhydramine and dimenhydrinate. Sedation is the most common side effect of these medications. Their anticholinergic effects might occasionally worsen gastroparesis.

Serotonin (5-HT3) receptor antagonists such as ondansetron and granisetron are very effective in controlling nausea and vomiting. They act both centrally and peripherally. They should be used only intermittently, as their long-term effects are unknown. They are also the most expensive of the antiemetic agents.

Prokinetic agents

Prokinetic agents (TABLE 3) enhance gastric contractility, correct dysrhythmias, and improve antroduodenal coordination. Usually, they should be given about 30 minutes before meals and at bedtime. Progress should be monitored by clinical improvement. Gastric emptying may not correlate very well with symptoms,[21] and hence monitoring by repeat emptying tests is not recommended. Elixirs are preferable to tablets and capsules to avoid problems related to poor emptying and erratic absorption.

Metoclopramide has both prokinetic and antiemetic properties, and hence is usually the first medication used in gastroparesis.[22] It stimulates release of acetylcholine from intrinsic cholinergic neurons and blocks peripheral dopamine receptors. The antiemetic effect is due to a central action on a chemoreceptor trigger zone. Maximum improvement is often seen within 1 month of starting treatment.

The limiting side effects of metoclopramide are due to antidopaminergic activity, occurring in 20% to 30% of patients. Acute dystonia is seen in up to 6% of patients, usually in the first 48 hours of starting the medication, particularly with high doses, and requires stopping the drug. Long-term efficacy has not been established due to tachyphylaxis.

Erythromycin acts as a motilin receptor agonist. Though it is the most potent prokinetic agent, there is no good evidence that it is better than other medications in improving symptoms. About 50% of patients report improvement in symptoms, but side effects such as nausea, vomiting, and abdominal pain can result in poor tolerance. Intravenous erythromycin is quite effective in acute exacerbations of gastroparesis,[23] particularly after surgery.

Cisapride is an agonist of the serotonin 5HT-4 receptor that facilitates acetylcholine release from cholinergic nerves.

The most serious side effect of cisapride is QT prolongation, which occasionally results in fatal cardiac dysrhythmias (torsades de pointes), particularly when this drug is combined with erythromycin. Cisapride has been withdrawn from the US market and is available only through special protocols.

Domperidone has a pharmacologic profile similar to that of metoclopramide. However, it does not cross the blood-brain barrier easily and has fewer central effects.[24] It has been studied mainly in patients with diabetic gastroparesis, and it is particularly helpful in

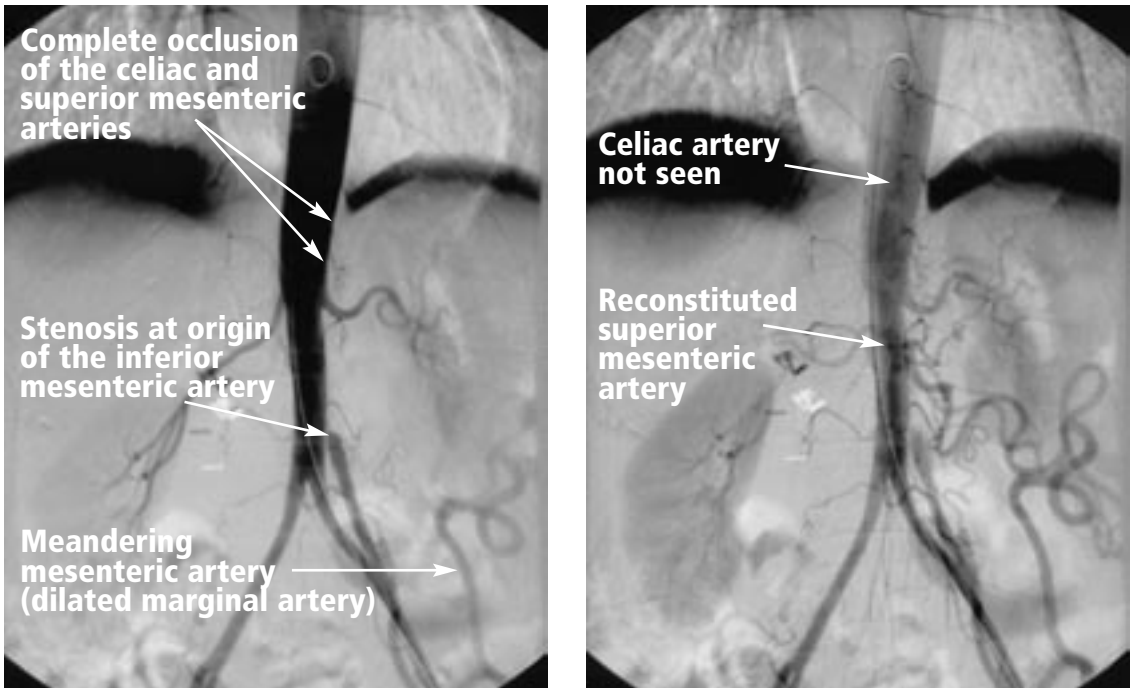

FIGURE 1. Mesenteric angiograms depicting markedly diminished blood flow in the gastric circulation.

patients who have not shown a good response to metoclopramide.

The main side effects of domperidone are due to increased prolactin levels, causing breast engorgement and galactorrhea. It is not approved by the US Food and Drug Administration (FDA), but it is available through specific pharmacies in the United States and in Canada.

Tegaserod is a partial agonist of the serotonin 5-HT4 receptor. It is currently FDA-approved for use in women with constipation-predominant irritable bowel syndrome. In addition, it has been shown to accelerate gastric emptying and small-bowel transit in healthy men,[25] although it is not FDA-approved for this indication.

In a recent study,[26] patients with symptomatic gastroparesis received either tegaserod in two dosages (6 mg three times a day or 12 mg twice a day) or placebo for 8 weeks. Tegaserod reduced gastric retention by half as measured at 4 hours. However, it is not clear if this improved gastric emptying translates into symptom improvement.

The main side effects of tegaserod are abdominal pain and diarrhea.

Newer therapies

Newer prokinetic agents include dopamine antagonists (levosulpiride)[27] and cholecystokinin antagonists (loxiglumide and its dextroisomer dexloxiglumide).[28] These investigational drugs have shown promising results in augmenting gastric emptying and improving symptoms.

Botulinum toxin injection in the pyloric sphincter decreases the sphincter tone and increases gastric emptying. A pilot study in 10 patients showed an almost 50% improvement in gastric emptying and a 38% improvement in symptom scores 4 weeks after injection of botulinum toxin 80 to 100 U in the pylorus.[29] This treatment has been used in patients with refractory diabetic and idiopathic gastroparesis, and the effect lasts several months.

Gastric electrical stimulation is being tried in patients with refractory gastroparesis. Electrical stimuli are delivered to the gastric

Prokinetic agents are given 30 minutes before meals and at bedtime

musculature at the greater curvature by an implantable device.

In a multicenter trial,[30] 33 patients received gastric electrical stimulators that were turned on or off in a randomized, double-blind crossover protocol for 2 months, followed by an open-label trial for 8 months. Vomiting and most other symptoms of gastroparesis decreased by 50% to 80%, even though emptying improved only modestly.[30] Five patients needed to have the stimulator removed or replaced owing to infection and other complications.

CASE CONTINUED

The patient was started on metoclopramide 10 mg four times a day and managed by her local physician. The response was transient, and she was switched to erythromycin, which also failed to provide a continued satisfactory response.

Two years later she still had symptoms, although not noticeably worse. She was referred once again to our department, this time for video capsule endoscopy to determine the cause of her abdominal symptoms. However, she was deemed unsuitable for capsule endoscopy due to her history of severe gastroparesis and markedly delayed small bowel transit.

To investigate her abdominal bruit, she underwent magnetic resonance angiography of the mesenteric vessels. This study revealed complete occlusion of the celiac trunk and the origin of the superior mesenteric artery, with distal reconstitution of blood flow. The inferior mesenteric artery was patent with a meandering mesenteric artery and a dilated marginal artery. A subsequent angiogram confirmed the findings (**FIGURE 1**).

The gastroparesis and delayed small bowel transit was presumed to be due to mesenteric ischemia. The patient underwent laparotomy with aortomesenteric bypass with a Hemashield graft to the common hepatic and superior mesenteric artery.

Within a few weeks her symptoms improved, and on follow-up 9 months later she had regained 20 pounds and was asymptomatic.

FINAL DIAGNOSIS: GASTROPARESIS DUE TO MESENTERIC ISCHEMIA

4 The diagnosis of chronic mesenteric ischemia is suggested by which of the following?

- ❑ Clinical symptoms of postprandial abdominal pain, weight loss, and fear of eating
- ❑ Angiographic demonstration of mesenteric arterial occlusion
- ❑ Exclusion of other gastrointestinal causes
- ❑ Response to revascularization
- ❑ All of the above

All of the above are correct.

Postprandial abdominal pain may be caused by chronic mesenteric ischemia, chronic pancreatitis, chronic cholecystitis, peptic ulcers, or gastroparesis. The pain of chronic mesenteric ischemia or "intestinal angina" occurs characteristically within an hour of eating and subsides in the next 2 to 3 hours. It is dull and crampy, and patients intentionally diminish food intake for fear of pain, which may result in severe weight loss.

Abdominal bruits are present in 50% of patients. Classically, angiography shows severe stenosis in at least two of the three major mesenteric vessels in a biplanar view.[31]

The combination of clinical history and angiographic findings strongly suggests chronic mesenteric ischemia, but in the absence of these classic features, other causes should be ruled out before attempts at revascularization.

Improvement of symptoms following revascularization offers the ultimate proof of the diagnosis of chronic mesenteric ischemia.

9 months after mesenteric bypass, she had regained 20 pounds and had no symptoms

DISCUSSION

The stomach is relatively resistant to ischemia, owing to a rich collateral blood supply from the celiac and superior mesenteric arteries. However, complete occlusion of these arteries may result in gastric ischemia and gastroparesis.

Kazimierz and Jacobson[32] reported that a reduction in blood flow to the bowel evokes initial increases in motility followed by prolonged inhibition of motor activity.

Liberski et al[33] reported the cases of two

TABLE 4

Features of ischemic gastroparesis as reported in the literature

FEATURE	NO. (N = 5)*
Women	5
Nausea, vomiting, weight loss, abdominal pain	5
Smoking	5
Documented abdominal bruit	2
Nonerosive gastritis	5
Poor response to medical therapy	5
Completely occluded celiac and superior mesenteric arteries	5 5
Complete resolution after revascularization	5

*Age range 48–60 years, mean age 55 years

middle-aged female smokers who had severe idiopathic gastroparesis for 6 and 18 months, respectively. Aortomesenteric bypass resulted in complete symptom resolution.

Casey et al[34] reported a retrospective series of seven patients, all female smokers age 41 to 71 years, who were diagnosed with gastric ischemia. All had histologically proven ulcerative gastritis, but only two had documented gastroparesis. Both women with gastroparesis had a good outcome after aortomesenteric bypass.

To our knowledge, only five cases (including ours) of gastroparesis due to mesenteric ischemia have ever been reported. All of them were in nondiabetic female smokers, and all five patients had an excellent response to revascularization (TABLE 4). All were thought to have had idiopathic gastroparesis for several months to years before the final diagnosis was made.

LESSONS FROM THE REVIEW

Gastroparesis is a gastric motility disorder resulting in functional gastric outlet obstruction. Women in the fourth decade are primarily affected. As the symptoms are nonspecific, a high index of suspicion is required. The solid-phase gastric emptying test is the gold standard to make the diagnosis of gastroparesis. Idiopathic and diabetic gastroparesis account for most cases (TABLE 1), but other causes should be sought. Treatment options are limited and may not have a good sustained response (TABLE 2, TABLE 3). Newer treatments offer some hope for people with this vexing problem.

Ischemia as a cause of gastroparesis is exceedingly rare. However, unlike other causes of gastroparesis, it may be completely cured by revascularization. Hence, we believe ischemia should be ruled out as a cause of idiopathic gastroparesis in female patients with an abdominal bruit, particularly those who also smoke (TABLE 4).

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