

CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

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Case 6-2005: A 58-Year-Old Man with Esophageal Cancer and Nausea, Vomiting, and Intractable Hiccups

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PRESENTATION OF CASE

Dr. Kevin R. McDonald: A 58-year-old man was transferred to this hospital for management of newly diagnosed adenocarcinoma of the esophagus.

Several months before admission, the patient initially had episodes of early satiety and then began to vomit all solid food. He lost 14 kg; light-headedness and dyspnea with minimal exertion developed. He did not have nausea, dysphagia, or odynophagia, but he was able to ingest only small amounts of liquids slowly without vomiting. Twelve days before admission, he went to the emergency department of another hospital.

An initial evaluation at that hospital revealed guaiac-positive stool, a hematocrit of 12 percent, a ferritin level of 2 ng per milliliter, a creatinine level of 6.1 mg per deciliter, and a positive test for hepatitis C antibody. Abdominal ultrasonographic examination showed bilateral hydronephrosis; chest and abdominal computed tomographic (CT) scanning without the administration of contrast material showed thickening of the distal esophagus extending into the fundus and the body of the stomach. Esophago-gastroduodenoscopy revealed an ulcerated, friable, and strictured distal esophagus and thickened mucosal folds throughout the stomach. An esophageal biopsy showed invasive adenocarcinoma with signet-ring features. The gastric biopsy showed no signs of carcinoma and was negative for the presence of *Helicobacter pylori*.

A Foley catheter was inserted, 6 units of packed red cells were transfused, and ferrous sulfate was administered. A proton-pump inhibitor and antibiotic therapy for an *Escherichia coli* urinary tract infection were instituted. While he was in the hospital, efforts to advance the patient's diet to purees produced vomiting, despite the administration of ondansetron and metoclopramide, and therefore, total parenteral nutrition was begun. The patient was transferred to this hospital.

The temperature was 36.5°C, the heart rate 64 beats per minute, the blood pressure 128/71 mm Hg, the respiratory rate 20 breaths per minute, and the oxygen saturation 100 percent while the patient was breathing ambient air. On physical examination, he was cachectic and frail, lying in bed, but not in acute distress. He appeared older than

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his stated age. Examination of the head, eyes, ears, nose, and throat disclosed pale conjunctivae, dry mucous membranes, and absent upper teeth. The remainder of the examination was normal. Laboratory-test results are shown in Table 1.

DIFFERENTIAL DIAGNOSIS

Dr. Brenna C. Bounds: Esophagogastroduodenoscopy with esophageal and gastric biopsies was performed on the second hospital day. There was marked thickening and friability of the tissue in the distal esophagus and thickening of the gastric mucosal folds, which were difficult to distend. This appearance is suggestive of a primary esophageal cancer extending into the gastric cardia.

Endoscopic ultrasonography was then performed. The stomach was floating in ascitic fluid, which was seen as an anechoic area between the transducer and the liver (Fig. 1A). A sample of the ascitic fluid was aspirated for cytologic examina-

tion. Endosonographic examination of the distal esophagus revealed thickening of the wall to 12 mm between the transducer of the echoendoscope and the outer portion of the wall; the normal esophagus is 2- to 3-mm thick in this area (Fig. 1B). The gastric wall was also markedly thickened at 13 mm (Fig. 1C). The normal five-layered struc-

Table 1. Laboratory-Test Results.*

Variable	Day 1 of Admission	Day 12	Day 27	Day 31
Sodium (mmol/liter)	149	147	139	138
Potassium (mmol/liter)	3.7	4.0	4.5	3.6
Chloride (mmol/liter)	115	112	104	102
Carbon dioxide (mmol/liter)	22.7	22.2	21.6	18.9
Urea nitrogen (mg/dl)	35	34	48	64
Creatinine (mg/dl)	2.1	1.8	1.8	2.8
Albumin (g/dl)	2.2		1.9	1.8
Direct bilirubin (mg/dl)	0.1	0.1	5.2	8.2
Total bilirubin (mg/dl)	0.3	0.2	7.8	13.5
Serum aspartate aminotransferase (U/liter)	15		374	360
Serum alanine aminotransferase (U/liter)	7		1113	986
Alkaline phosphatase (U/liter)	55		799	907
Prostate-specific antigen (ng/ml)	2.1			
Ferritin (ng/ml)	34			
Hematocrit (%)	27.6			
Hemoglobin (g/dl)	8.9			
White cells (per mm ³)	3,900			
Platelets (per mm ³)	225,000			

* To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

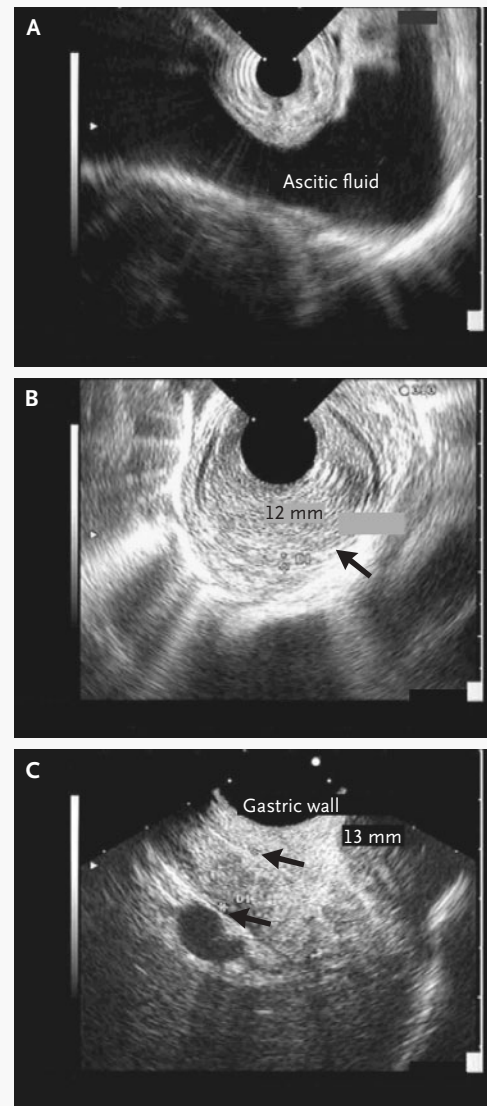


Figure 1. Endoscopic Ultrasonographic Images.

The stomach is floating in ascitic fluid (black area, Panel A). There is thickening of the esophageal wall to 12 mm (arrow, Panel B); normal is 2 to 3 mm. There is thickening of the gastric wall to 13 mm (arrows) due to the extension of the esophageal cancer into the gastric cardia (Panel C).

ture of the gastric wall was obliterated, resulting in a homogeneous, hypoechoic appearance on endoscopic ultrasonography. The infiltrate did not extend through the serosal surface or invade adjacent organs.

Dr. Dushyant Sahani: An abdominal ultrasonographic study performed on the second hospital day showed bilateral upper urinary tract ectasia with renal cortical thinning, suggestive of chronic reflux disease. A review of a magnetic resonance imaging study of the abdomen performed at the other hospital revealed no liver lesions or lymphadenopathy. Repeated chest and abdominopelvic CT scanning without the administration of intravenous contrast material on the ninth hospital day (Fig. 2) confirmed the thickening of the lower esophagus, the gastroesophageal junction, and the lesser curvature of the stomach. There was no evidence of bowel obstruction. Contiguous extension of the tumor into the gastrohepatic ligament was evident.

PATHOLOGICAL DISCUSSION

Dr. Elena F. Brachtel: The specimen from the esophageal biopsy (Fig. 3A) shows Barrett's mucosa adjacent to esophageal squamous epithelium and invasive tumor extending from the deep mucosa into the submucosa and infiltrating through the muscularis of the esophageal wall. Barrett's mucosa is

characterized by replacement of the esophageal squamous epithelium by columnar epithelium with specialized intestinal cells (goblet cells) (Fig. 3A). The metaplastic epithelium may show intraepithelial neoplasia with cytologic atypia. In this case, densely arranged glands with crowded, irregular, and hyperchromatic nuclei represent high-grade epithelial dysplasia (Fig. 3B). The adenocarcinoma cells often show cytoplasmic mucin and a flattened, peripheral nucleus, the hallmark of signet-ring cells (Fig. 3C). This is an invasive, poorly differentiated adenocarcinoma of the signet-ring cell type arising on a background of Barrett's mucosa with high-grade dysplasia.

Adenocarcinoma of the esophagus is increasing in incidence in the United States.¹ The most important precursor lesion is Barrett's esophagus, the transformation of the squamous epithelium lining the esophagus into glandular intestinal epithelium, owing to acid reflux from the stomach. Risk factors associated with squamous-cell carcinomas of the esophagus — smoking and ethanol ingestion — are not associated with adenocarcinoma. The majority of esophageal adenocarcinomas are moderately differentiated to well differentiated. Cancers with signet-ring cell features are rare, reported in only about 6 percent of cases of esophageal adenocarcinoma.²

Biopsy specimens from the stomach and duodenum did not contain tumor; however, the presence of tumor in the deeper layers of the wall could not be ruled out, since these areas were not sampled. Diffusely infiltrating adenocarcinomas may involve the wall of the stomach extensively without infiltrating the overlying mucosa.

The cytologic specimen of the ascitic fluid was positive for adenocarcinoma (Fig. 3D).

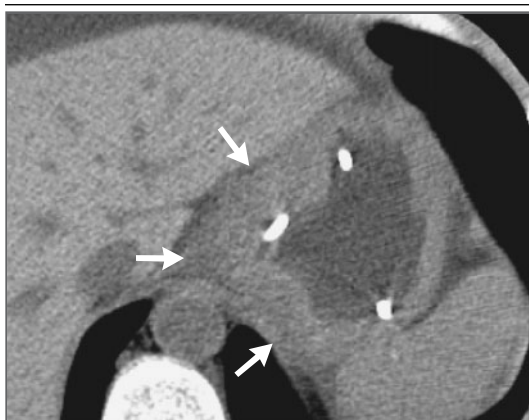


Figure 2. CT Scans of the Abdomen Performed without Intravenous Injection of Contrast Material.

An image through the stomach shows soft-tissue thickening of the gastric wall along the lesser curvature (arrows); there was contiguous extension of the soft-tissue abnormality into the gastrohepatic ligament.

DISCUSSION OF MANAGEMENT

Dr. Andrew X. Zhu: Esophageal cancer of either of the two major histologic types is aggressive, with a dismal prognosis. Survival depends on the stage of disease at diagnosis.³ Five-year survival rates range from 28 percent among patients with localized cancer to 12 percent and 2 percent for those with regional and distant disease, respectively. On the basis of the positive cytologic evaluation of the ascitic fluid, this patient had stage IV disease with peritoneal metastases.

Treatment of esophageal carcinoma is based on the clinical presentation and extent of disease, a

careful weighing of the potential benefits and toxic effects of each treatment, and the available institutional resources and expertise. Although systemic chemotherapy can be effective, it can be given only to patients with an adequate performance status — ambulatory and capable of most self-care — and nutritional status. Surgical esophageal-bypass procedures provide limited benefit and are associated with substantial morbidity in patients with clearly unresectable disease. Radiation therapy given alone or in combination with chemotherapy has an important role in palliation of dysphagia or for local disease control, as do endoscopic palliative procedures such as dilation, laser therapy, stenting, and photodynamic therapy.

This patient had several disease-related symp-

toms, including vomiting after eating, severe anemia, and cachexia, but no clinically significant dysphagia. Because of his poor nutritional and performance status, I recommended that the initial focus of his care should be on improving his nutrition and optimizing the management of his symptoms before chemotherapy or radiation therapy was considered.

Dr. McDonald: On the fifth hospital day, hiccups, nausea, spontaneous vomiting, and abdominal pain exacerbated by retching developed; these symptoms rapidly worsened over the next several days. The patient's pain was relieved by low doses of morphine, but the hiccups, nausea, and vomiting were refractory to a regimen consisting of 8 mg of ondansetron given intravenously every eight hours,

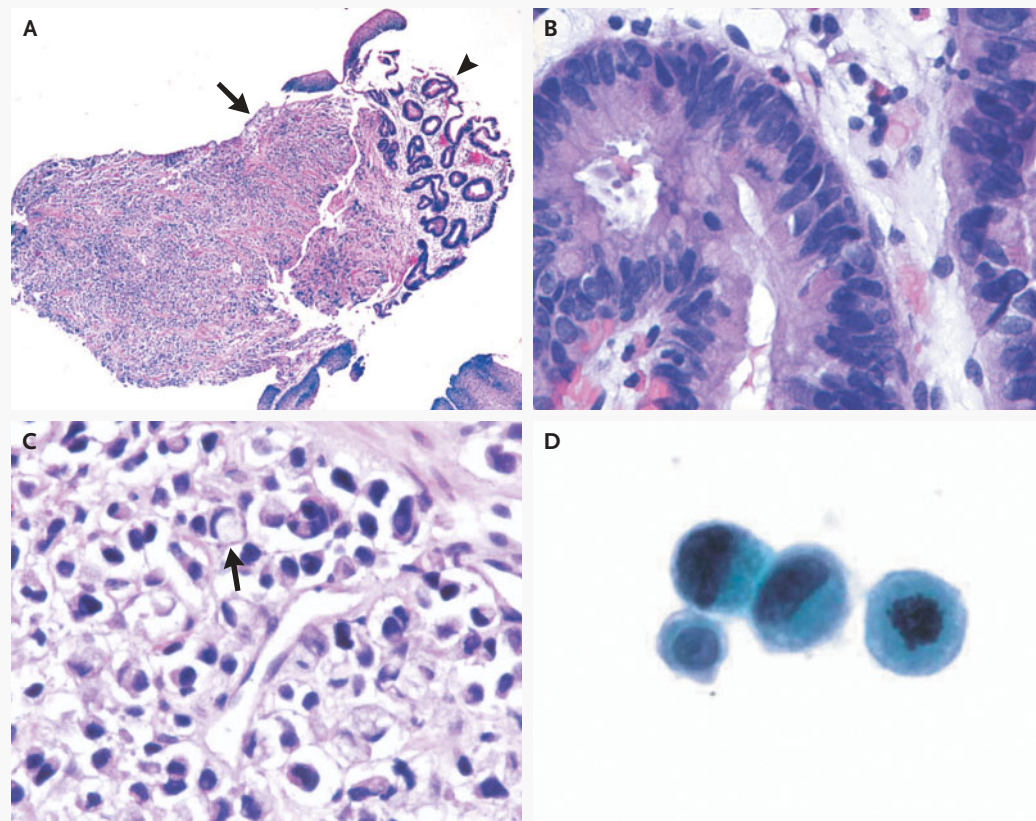


Figure 3. Esophageal-Biopsy Specimen (Hematoxylin and Eosin) and Cytologic Specimen of Ascitic Fluid (Papanicolaou Stain).

Panel A shows the esophageal adenocarcinoma infiltrating the mucosa into deeper layers of the esophageal wall (arrow). The mucosal surface consists of Barrett's mucosa (arrowhead) and a few fragments of squamous epithelium; the Barrett's mucosa focally shows high-grade dysplasia, with nuclear crowding and atypia of the glandular epithelium (Panel B). Higher magnification of the invasive esophageal adenocarcinoma (Panel C) reveals sheets of tumor, some with signet-ring features (arrow). Panel D shows tumor cells in the ascitic fluid.

50 mg of ranitidine given intravenously every eight hours, 10 mg of metoclopramide given intravenously every six hours as needed, suppositories containing 25 mg of promethazine given rectally every six hours as needed, 1 to 2 mg of lorazepam given intravenously every two hours as needed, 25 mg of chlorpromazine given by way of a nasogastric tube four times daily as needed, and 15 mg of baclofen given by way of a nasogastric tube three times daily as needed.

Efforts to provide enteral feeding were thwarted by vomiting, which caused expulsion of two nasogastric tubes and three nasojejunal feeding tubes. Surgical consultants were of the opinion that neither resection of the tumor nor placement of a jejunostomy tube was feasible because of the presence of malignant ascites and the extent of the tumor in the esophagus and stomach.

On the 12th hospital day, while awaiting opinions from medical and radiation-oncology consultants, consultants from the palliative care service were asked to assist with the management of the refractory hiccups, nausea, and vomiting and to help the patient with the process of making end-of-life decisions. At this initial meeting with the palliative care service team, the patient appeared disheveled, agitated, and cachectic and was sitting up in bed hiccuping and vomiting frequently and violently into a basin. The incessant hiccups, nausea, and vomiting kept him confined to his room and prevented sleep. He had not moved his bowels in several days. He was exhausted, demoralized, and miserable, and he was dismissive of the hospital staff because he felt they could not help him.

We obtained the additional information that he lived in a small town 50 miles away. He had worked at a local market, had no health insurance, and had had no medical care for more than a decade. He lived with his dog and an elderly companion. He continued to smoke one pack of cigarettes per day, as he had for 40 years. He rarely drank alcohol, had never used intravenous drugs, and had not previously received blood products. The results of the physical examination were unchanged from the evaluation at the time of admission. Laboratory-test results are shown in Table 1.

On the basis of the initial evaluation by the consultants from the palliative care service, ondansetron was discontinued and metoclopramide was given around the clock instead of as needed for vomiting. Chlorpromazine was continued (orally, intramuscularly, or in rectal suppositories) as

needed for hiccups, and 15 ml of senna given orally twice daily and 10 to 20 mg of bisacodyl in rectal suppositories daily as needed were ordered for constipation. On this regimen, the patient moved his bowels, but there was no improvement in his hiccups, nausea, or vomiting, and he began to report dyspnea when the hiccuping or vomiting was most severe.

ACUTE PALLIATIVE CARE

Dr. Eric L. Krakauer: When the palliative care service was initially consulted, it was not clear what treatment options would be available for this patient's cancer, and the goals of care had not yet been clearly established. Regardless of the goals, the severity and refractory nature of the patient's nausea and vomiting called for an immediate and aggressive symptom-oriented response.⁴

In spite of this patient's severe symptoms, a brief, frank discussion was possible. First, sitting at his bedside, we assured him that his symptoms could be treated aggressively and that he did not need to suffer. After this expression of concern and reassurance, the patient was no longer dismissive. We were able to elicit enough information about his most important goals and values to know what treatments were most appropriate and what risks of side effects were acceptable to him. The patient wanted relief of his symptoms and wanted to be comfortable, even if sedation was required. If possible, he also hoped to be able to return home. We assured him that we would make every effort to get him home.

DIFFERENTIAL DIAGNOSIS OF NAUSEA AND VOMITING IN PATIENTS WITH CANCER

The selection of the most effective treatment for this patient's nausea, vomiting, and hiccups depended on an understanding of the pathogenesis of these acutely distressing symptoms. When the cause of symptoms such as these is not obvious, a thorough differential diagnosis should be undertaken.

Nausea is a subjective sensation that precedes vomiting. It is caused by stimulation of one or more of four sites: the gastrointestinal tract, the vestibular system, the chemoreceptor trigger zone in the area postrema of the floor of the fourth ventricle, and higher centers in the central nervous system (CNS). Vomiting is the forceful expulsion of gastric contents by a complex neuromuscular process with voluntary and involuntary components.⁵ One or more of the four sites involved in nausea stimulates

the nucleus of the tractus solitarius and the reticular formation of the medulla oblongata, which make up the vomiting center (Fig. 4).⁶ The vomiting center acts as the final common pathway by initiating parasympathetic and motor-efferent activity that produces vomiting. In order to palliate this patient's nausea optimally, we needed to determine which of these four sites was responsible.

The chemoreceptor trigger zone, where the blood-brain barrier is thought to be absent or ineffective, is stimulated by way of dopamine type 2 receptors by blood-borne toxins. These toxins may be endogenous or exogenous. Endogenous toxins may be elaborated by neoplasms or may result from conditions common in patients with cancer, such as renal or hepatic failure, hypercalcemia, hyponatremia, and sepsis. Exogenous toxins include opioid and cytotoxic chemotherapeutic medications or bacterial toxins. When the chemoreceptor trigger zone is activated, efferent stimuli in turn activate the vomiting center. This patient had not received chemotherapy for the cancer, but he had received an opioid agent for pain and he had acute renal failure related to obstructive nephropathy from blockage of the bladder outlet. The drug or the renal failure could be causing nausea through this pathway.

The gastrointestinal tract and heart can activate the vomiting center by the stimulation of mechanoreceptors or chemoreceptors on vagal or glossopharyngeal afferents. Drugs such as opioid agents and those with anticholinergic effects cause constipation, which can stimulate vagal mechanoreceptors and result in vomiting. Mucosal irritants, such as nonsteroidal antiinflammatory drugs, also can stimulate vagal afferents. Cytotoxic chemotherapeutic agents and radiation therapy can produce emesis by causing the release of serotonin from enterochromaffin cells in the gut, resulting in stimulation of 5-hydroxytryptamine type 3 receptors on vagal afferents. Emetogenic stimulation of the vagus or glossopharyngeal nerves can have other causes as well. These include local irritation of the pharynx, esophagus, or stomach by infection, gastroesophageal reflux, radiation therapy, or ethanol; delayed gastric emptying due to medications, tumor, inflammation, ascites, or autonomic dysfunction; stretching of the serosa due to liver metastases or obstruction of the gastric outlet or bowel; ileus due to drugs, ascites, or autonomic dysfunction; and cardiac ischemia. During his hospital course, this patient had constipation, esophageal ir-

ritation, ascites, and delayed gastric emptying — all of which could have contributed to nausea by way of these pathways.

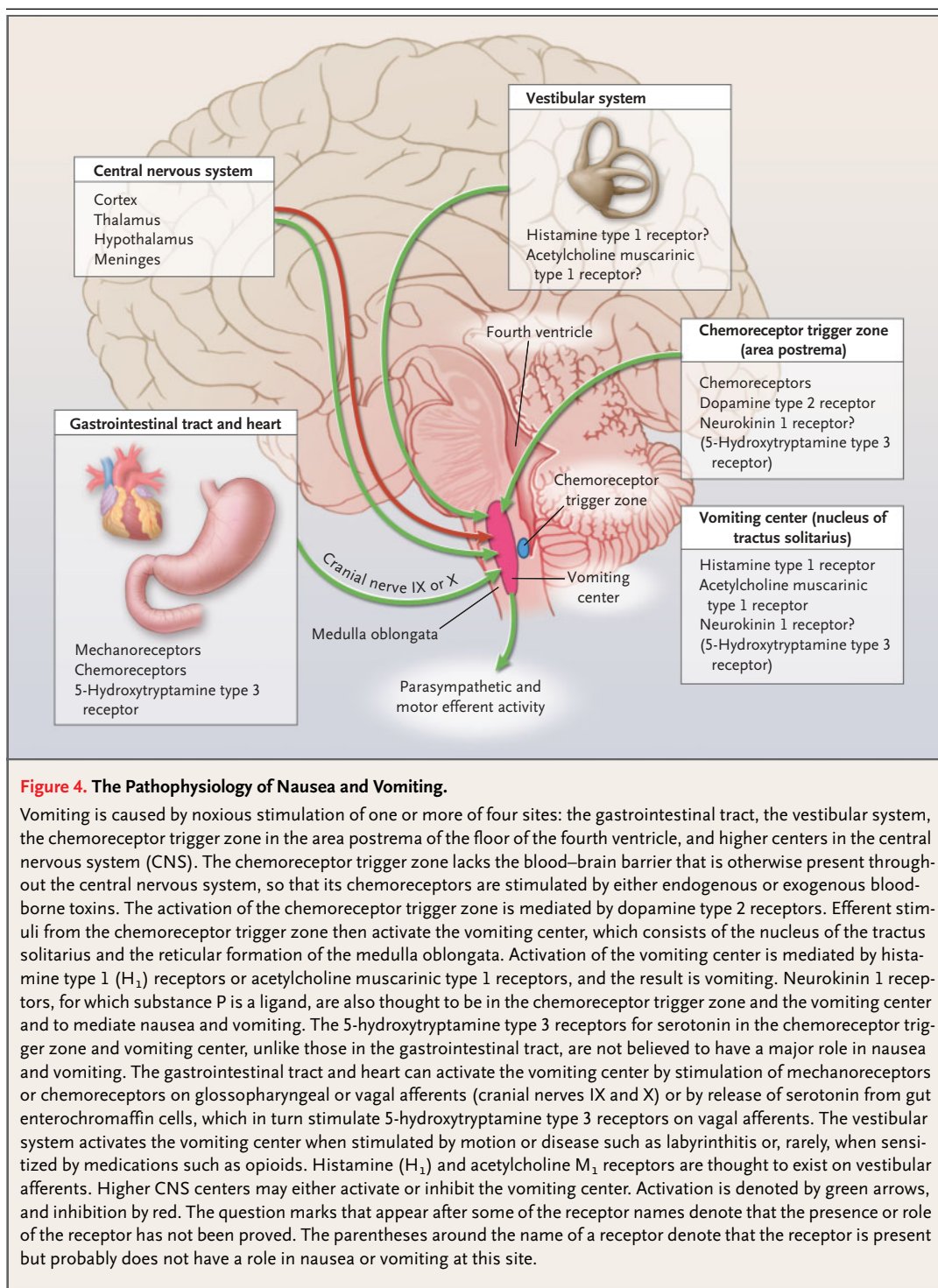
The vestibular system activates the vomiting center when stimulated by motion or disease such as labyrinthitis or, rarely, when sensitized by medications such as opioid agents. Higher centers of the CNS can either activate or inhibit the vomiting center. CNS conditions that can activate the vomiting center include increased intracranial pressure (from CNS metastases, for example), meningeal irritation due to cancer or infection, anxiety, anticipation of emetogenic chemotherapy, and migraine. This patient's nausea and vomiting did not appear to be caused by a disorder of the nervous system.

Because of this patient's goals and acute symptoms, the initial history taking and physical examination were brief and directed at uncovering the cause of his symptoms. Our assessment of this patient was that his esophageal adenocarcinoma with gastric linitis plastica (malignant infiltration of the gastric wall; also called leather bottle stomach) was disrupting peristalsis and causing a functional gastric-outlet obstruction and that this was resulting in intractable vomiting.^{7,8} Efforts at palliation were initiated immediately.

DIFFERENTIAL DIAGNOSIS OF HICCUPS IN CANCER PATIENTS

Dr. McDonald: Hiccups are repeated spasms of the diaphragm followed by sudden closure of the glottis. The medical term, singultus, derives from the Latin, meaning a gasp or a sigh. Episodes are usually brief and self-limited. Persistent hiccups (episodes lasting more than 48 hours) or intractable hiccups (episodes lasting more than one month) can cause anorexia, weight loss, disabling sleep deprivation, anxiety, and depression.^{9,10}

The pathophysiology of hiccups is not well understood. The hiccups reflex arc consists of an afferent pathway — the vagus or phrenic nerve or the sympathetic ganglia — a connection that is made either in the spinal cord or at higher CNS levels and an efferent pathway, the phrenic nerve.¹¹ Hiccups are probably most often due to stimulation or irritation of the afferent limb or of the CNS centers that control the diaphragm. Distention or inflammation of the esophagus, stomach, liver, or other organs can stimulate vagal afferents, and tumor or abscess may directly irritate the vagus or phrenic nerves, the diaphragm, or CNS centers. Toxic and metabolic causes of hiccups include uremia, hypo-



natremia, hypokalemia, hypocalcemia, ethanol ingestion, and some medications, including chemotherapeutic agents. Hiccups also can be psychogenic.¹² The palliative care team thought that this

patient's severe persistent hiccups were probably due to stimulation of the vagus nerve as a result of gastric distention or to direct irritation of the vagus or phrenic nerves by tumor.

DISCUSSION OF MANAGEMENT

Dr. Krakauer: It was not surprising that this patient's vomiting was refractory to the serotonin antagonist ondansetron, since he had had no surgery, chemotherapy, or radiation therapy that might cause the release of serotonin from intestinal enterochromaffin cells.¹³ We gave him 8 mg of dexamethasone intravenously every 12 hours for several reasons. We hoped to reduce inflammation in the gastric wall caused by tumor infiltration and thereby perhaps to improve peristalsis. We also hoped to reduce possible irritation of the phrenic nerve by tumor. In addition, dexamethasone can be effective in treating vomiting due to emetogenic toxins.¹⁴ Since the butyrophenone haloperidol is a more potent dopamine type 2 receptor antagonist and antiemetic than the phenothiazines (for example, chlorpromazine or prochlorperazine) and since it appears to be as effective as the phenothiazines for hiccups, we also added 5 mg of haloperidol given intravenously every six hours to the patient's medications.^{6,11} We continued metoclopramide, ranitidine, senna, and morphine as needed for pain.

Within 24 hours of the beginning of this regimen, the patient's hiccups almost completely resolved, and there were no extrapyramidal side effects. However, his vomiting became even more frequent and, for the first time, bilious. Thus, the functional obstruction appeared to be at the level of the duodenum rather than the gastric outlet. In response, we began therapy with octreotide, a somatostatin analogue that inhibits exocrine and endocrine secretion in the gastrointestinal tract.^{15,16} We gave a 50- μ g intravenous bolus of octreotide, started an intravenous drip of octreotide at 50 μ g per hour, and continued the previously described regimen of drugs at the same doses. The next day, the patient felt much better. His hiccups, nausea, and vomiting had resolved. He had had only two episodes of minimal regurgitation since the octreotide was started, and he reported feeling hungry for the first time in weeks.

Once the patient's symptoms were controlled, a more detailed social history and a more thorough discussion of his values and goals were possible. His only family members lived in a distant state, and he had not seen them for many years. He was not religious. His greatest joys were being with his friends and his dog, reading novels and news of current events, and smoking. We discussed the pos-

sibility that vomiting, hiccups, pain, or other symptoms could recur, and he confirmed that his primary goals were comfort and the best possible quality of life until his death. He was willing to accept partial or complete sedation if necessary to be comfortable. His secondary goals were to get back to his hometown to see his dog and friends and to regain enough strength to tolerate treatment of his cancer.

We assured the patient that a level of comfort acceptable to him would be maintained by any means necessary, including sedation, and that we would make every effort to transfer him to a facility in his hometown that could ensure his comfort.¹⁷ We recommended that a social worker see the patient and that physical therapy be initiated to give him every opportunity to improve his strength and functional status. We also recommended, on the basis of the patient's goals and values as he had expressed them and given the very poor outcome of cardiopulmonary resuscitation in patients with advanced cancer,¹⁸ that he be protected from resuscitation in the event of cardiac or respiratory arrest. As a result of these discussions, a "no cardiopulmonary resuscitation" order was written at the patient's request, and social-work and physical-therapy interventions began.

The patient remained in the hospital for three more weeks, primarily because his lack of health insurance and continuing total parenteral nutrition made it difficult to find a suitable facility in his hometown that would accept him. Three days after the octreotide therapy was initiated, a single 30-mg depot injection of octreotide was given intramuscularly, and the intravenous drip was then tapered over a two-week period.

The treatment plan was to continue monthly depot injections of octreotide as long as the drug effectively controlled the patient's vomiting and no unacceptable side effects developed. The dexamethasone dose was tapered very slowly to 2 mg given intravenously every 12 hours, and the metoclopramide, haloperidol, ranitidine, and senna were continued. During this period, the patient had mild intermittent hiccups and regurgitation without nausea or vomiting. Mild jaundice developed, and there was an increase in the level of liver transaminases (Table 1), but he had no abdominal pain or other symptoms attributable to the liver or biliary system.¹⁹ He was able to sleep, sip liquids, read, and go outside in a wheelchair to smoke. With psycho-

social support and encouragement, he called his long-estranged mother and brother to reconcile and say good-bye.

In spite of total parenteral nutrition and physical therapy, the patient's strength and performance status did not improve. Total parenteral nutrition was discontinued both because it appeared to provide no benefit and because it complicated discharge planning. The patient finally was accepted by an inpatient hospice in his hometown and he was discharged. He visited with his friends and his dog at the hospice and died comfortably three days after he was discharged from this hospital.

Dr. Nancy Lee Harris (Pathology): I was curious about the definition of intractable hiccups as lasting more than four weeks. That sounds like a long time.

Dr. Krakauer: That is the definition given in the literature, but I agree: four hours would be enough for me to consider hiccups intractable.

Dr. J. Andrew Billings (Palliative Care): This is probably the first clinicopathological conference in which notation of the presence of a beloved pet in the home was not intended to suggest a potential animal vector of disease but, rather, was included as important psychosocial information about the patient and his goals for care. I believe Richard Cabot, who not only founded these discussions of case records but also emphasized the importance of understanding our patients' backgrounds and helped found the field of medical social work, would have been proud.

FINAL DIAGNOSIS

Adenocarcinoma of the esophagus with gastric linitis plastica and functional duodenal obstruction.

Dr. Krakauer is a Faculty Scholar of the Open Society Institute's Project on Death in America.

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SLIDE SETS FOR THE CASE RECORDS AVAILABLE IN DIGITAL FORMAT

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