A SELF-TEST OF CLINICAL RECOGNITION

CME CREDIT

KAVITA R. KONGARA, MD
Department of Gastroenterology, Cleveland Clinic; research interests in gastrointestinal motility disorders

DARWIN L. CONWELL, MD
Department of Gastroenterology, Cleveland Clinic; research interests in acute recurrent pancreatitis and chronic pancreatitis

Upper gastrointestinal bleeding in a 41-year-old woman

A 41-YEAR-OLD WOMAN presents to the emergency department with epigastric pain, dyspnea, and tarry stools. Four months ago she had developed hemorrhagic gastritis while taking ibuprofen, and received omeprazole for 6 weeks as treatment. However, she says she has not taken any nonsteroidal anti-inflammatory agents recently.

The patient is hemodynamically stable, although she has an orthostatic blood pressure change—her blood pressure is 106/60 mm Hg in the sitting position and falls to 90/58 mm Hg upon standing. Examination of the heart, lungs, and abdomen is normal. Her stool is brown and heme-negative. She is admitted to the hospital under the care of the gastroenterology service, with plans for an upper endoscopy to be performed the next day.

However, the next day, as soon as the endoscope is inserted, the patient vomits a massive amount of blood and becomes hemodynamically unstable. Her physician inserts an endotracheal tube, gives her intravenous fluids for resuscitation, and performs a gastric lavage, obtaining 600 mL of bloody clot.

When the physician inserts the endoscope again, she discovers large gastric varices (FIGURE 1). Of note, there are no esophageal varices, and one gastric varix has an adherent clot, indicating a recent site of bleeding. The physician orders intravenous octreotide and a transfusion of packed red cells, and obtains a surgical consultation.

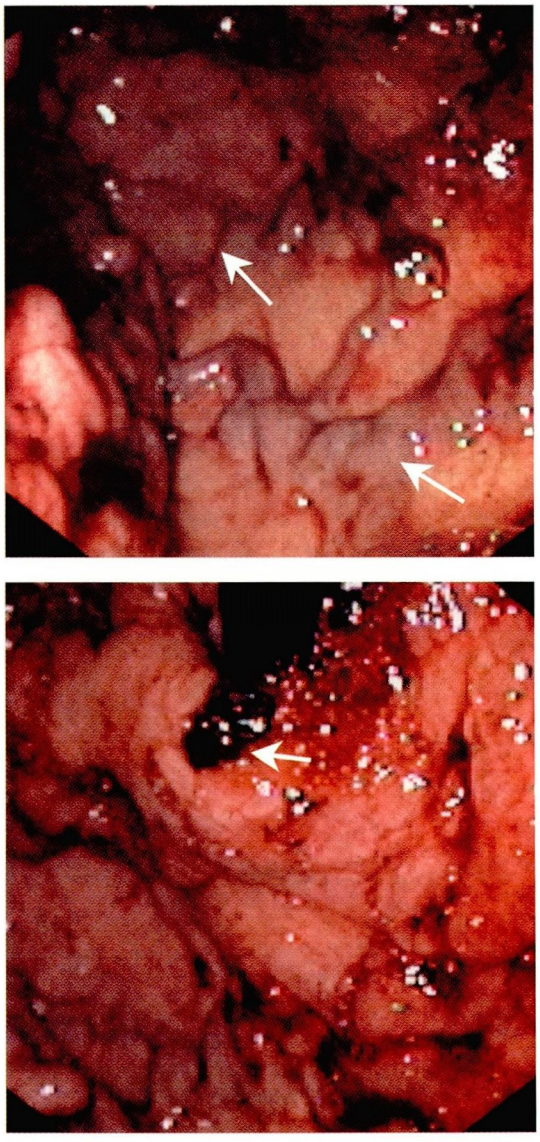

FIGURE 1. Gastric varices. Top, arrows point to multiple fundic varices; bottom, retroscopic retroflexed view of a bleeding gastric varix with an adherent clot (arrow).

Isolated gastric varices suggest thrombosis in the splenic or portal vein

VARICES IN THE STOMACH, BUT NOT THE ESOPHAGUS

1 Which of the following could be the cause of this patient's gastric varices?

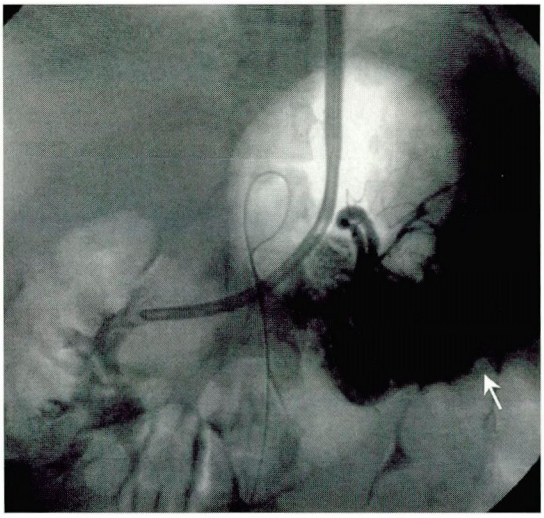

FIGURE 2. Visceral angiogram. Selective splenic artery injection showing a hypervascular mass overlying the pancreatic tail (arrow).

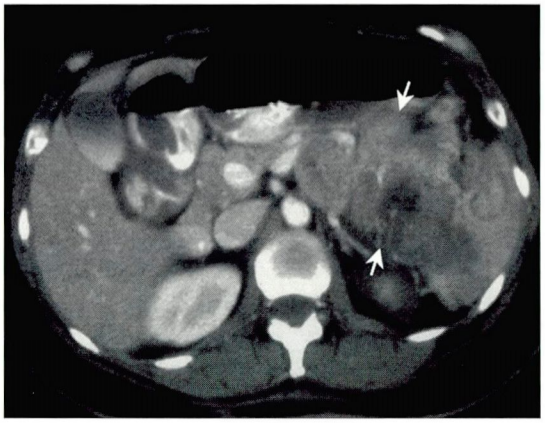

FIGURE 3. Computed tomographic scan of the abdomen. Arrows point to a large, enhancing left upper-quadrant mass arising from the pancreas.

- ❑ Splenic vein thrombosis
- ❑ A pancreatic mass
- ❑ Portal vein thrombosis
- ❑ A hypercoagulable state
- ❑ All of the above

Isolated gastric varices (ie, those confined to the stomach) characteristically suggest thrombosis in the splenic or portal vein. The possible causes of thrombosis in these locations include pancreatic cancer, pancreatitis, and a hypercoagulable state. In contrast, esophageal varices are usually due to cirrhosis of the liver.

The patient required multiple blood transfusions. On the recommendation of the surgeon, she underwent angiography to confirm the source of bleeding. The angiogram showed splenic vein thrombosis with secondary gastric varices. Also noted on the angiogram was extrinsic compression and encasement of distal splenic arterial branches, suggestive of a pancreatic tumor (FIGURE 2).

IMAGING THE PANCREATIC TUMOR

2 Given the findings described above, what is the imaging study of choice?

- ❑ Computed tomography
- ❑ Ultrasonography
- ❑ Magnetic resonance imaging
- ❑ None of the above

Computed tomography (CT) would provide the most anatomical information to define the source of the extrinsic compression implied by the angiographic findings. This patient's CT scan disclosed a large, hypervascular, left upper-quadrant mass presumably arising from the pancreas, and a splenic vein thrombosis (FIGURE 3). The liver appeared normal.

The patient continued to bleed, and was taken to the operating room. Exploratory laparotomy revealed a large mass at the body and tail of the pancreas extending to the splenic hilum and greater curvature of the stomach. Frozen-section analysis indicated the mass was a high-grade neuroendocrine tumor. No metastases were detected.

TREATING A PANCREATIC NEUROENDOCRINE TUMOR

3 What is the best therapy for this neuroendocrine tumor at this point?

- ❑ Chemotherapy
- ❑ Radiation therapy
- ❑ Distal pancreatectomy and splenectomy
- ❑ Palliation (none of the above)

Pancreatic neuroendocrine (islet cell) tumors have a prevalence of less than 1 per 100,000 population.[1,2] Most do not develop from islet cells directly but from pluripotential neuroen-

Consider octreotide, lanreotide, or interferon alfa for inoperable, functional tumors

TABLE 1

Neuroendocrine tumors of the pancreas

TUMOR TYPE	HORMONAL PRODUCT	USUAL SIZE	MALIGNANCY RISK	CLINICAL PRESENTATION	% LOCATED IN THE PANCREAS
Insulinoma	Insulin	Small	Small	Neuroglycopenia, catecholamine excess	97
"VIPoma"	Vasoactive intestinal polypeptide	Large	60%–90%	Watery diarrhea	90 (adults)
Glucagonoma	Glucagon	Large	60%–90%	Rash, anemia, weight loss, glucose intolerance	Almost 100
Somatostatinoma	Somatostatin	Large	60%–90%	Gallstones, diarrhea, steatorrhea, glucose intolerance	56
"GRFoma"	Gonadotropin-releasing factor	Large	60%–90%	Acromegaly	30
"PPoma"	Pancreatic polypeptide	Large	60%–90%	Mass effects	Most*
Nonfunctional	None	Large	60%–90%	Mass effects	Most*

*Data are limited

SOURCE: ADOPTED FROM METZ, REFERENCE 2

docrine stem cells located within exocrine pancreatic ductules.[2] They are indolent and slow-growing, making the diagnosis difficult in many cases (TABLE 1).

Most patients present with features caused by excess production of a single hormone such as insulin or gastrin. Others have nonfunctional tumors, and some have tumors that secrete several hormones.[1,3,4]

For all types of pancreatic neuroendocrine tumors, the general principles of treatment are to control the neuroendocrine syndrome (in cases that involve excess secretion of a functional hormone) and to surgically resect all resectable tumors.[2,5] Given the choices above, the best treatment at this time would be a distal pancreatectomy and splenectomy.

WHAT TYPE OF NEUROENDOCRINE TUMOR?

4 To differentiate the type of neuroendocrine tumor, which of the following serum levels should be measured?

- ❑ Insulin
- ❑ Gastrin
- ❑ Glucagon
- ❑ Vasoactive intestinal polypeptide
- ❑ Pancreatic polypeptide
- ❑ All of the above

PPomas are considered nonfunctional

Because the patient had no symptoms of hormone excess before her admission, the tumor is most likely nonfunctional. However, all of the above would help to rule out the other possibilities. This patient had normal levels of all of these substances except for a pancreatic polypeptide level of 2,024 pg/mL (normal: 64–243 pg/mL). Therefore, she most likely has a pancreatic polypeptide-producing tumor (or "PPoma").

Although PPomas produce pancreatic polypeptide, they do not cause clinical symptoms except for mass effects and are therefore considered nonfunctional.[6] In this case, as in others in the literature, the tumor caused a splenic vein thrombosis (by compression), which led to left-sided portal hypertension with resultant isolated gastric varices and massive upper gastrointestinal bleeding.[7]

The primary therapy is surgical resection. If an islet cell tumor is inoperable and functional, then octreotide, lanreotide, or interferon alfa can be considered.[8] If the tumor pro-

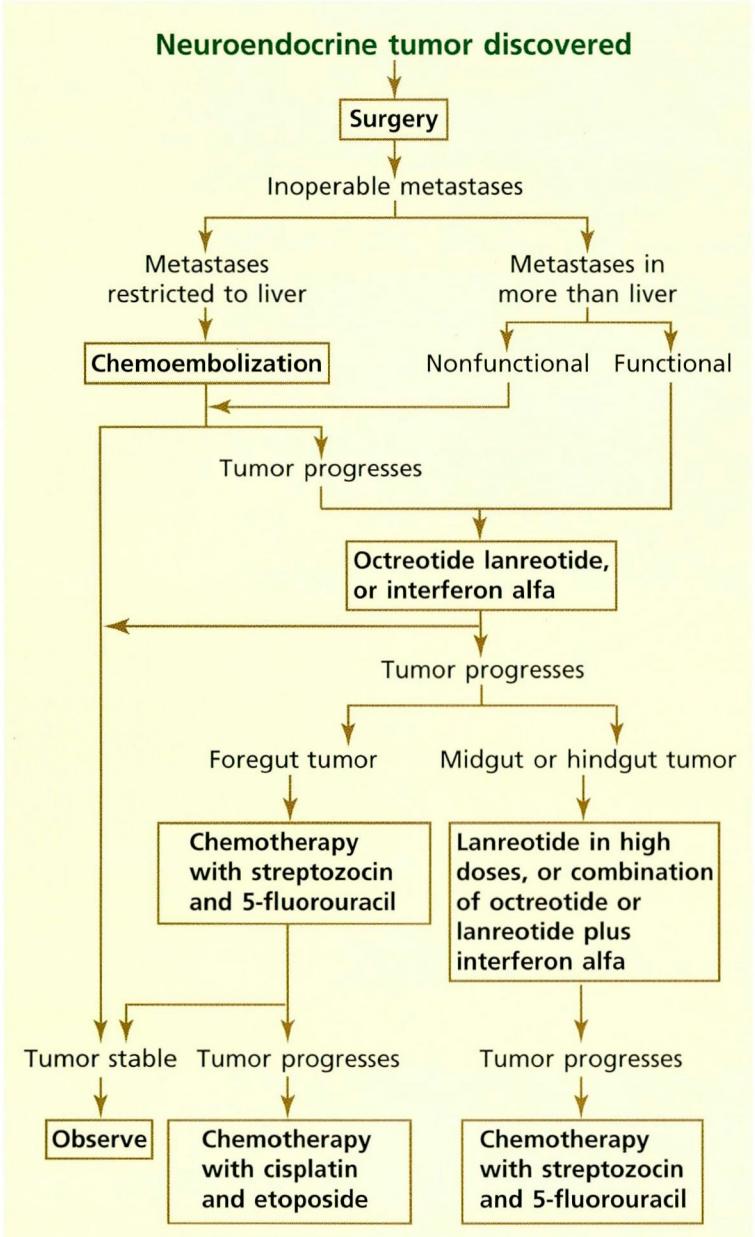

FIGURE 4. Proposed algorithm for treating pancreatic neuroendocrine tumors.
SOURCE: ADAPTED FROM FAISS ET AL, REFERENCE 5.

gresses, then combination chemotherapy with streptozocin and 5-fluorouracil is the treatment of choice (FIGURE 4).[5] In cases with metastases restricted to the liver, chemoembolization has been tried. This procedure consists of injecting a chemotherapeutic agent into an artery leading into the tumor, and then injecting an embolus of foam or gel to retain the drug in the tumor and to cause ischemia. Because our patient's tumor was operable and nonfunctional, there was no indication for using octreotide.[9]

The 5-year survival rate for patients with nonfunctional tumors ranges from 35% to 63%.[1] Patients with functional tumors have a similar prognosis; however, they may present at an earlier stage because of systemic effects of hormone excess.[5]

For inoperable tumors, chemotherapy with streptozocin and 5-fluorouracil relieves symptoms in up to 60% of patients.[1] Endoscopic ultrasonography and somatostatin receptor scintigraphy detect tumors with great sensitivity and can be useful to rule out recurrence of islet cell tumors.[10,11]

REFERENCES

1. **Cheslyn-Curtis S, Sitaram V, Williamson RCN.** Management of non-functioning neuroendocrine tumours of the pancreas. Br J Surgery 1993; 80:625–627.
2. **Metz D.** Diagnosis and treatment of pancreatic neuroendocrine tumors. Semin Gastrointest Dis 1995; 6:67–78.
3. **Kent RB, Van Heerden J, Weiland L.** Nonfunctioning islet cell tumors. Ann Surg 1980; 193:185–190.
4. **Closset J, Delhaye M, Sperduto N, et al.** Nonfunctioning neuroendocrine tumors of the pancreas: Clinical presentation of 7 patients. Hepatogastroenterology 1996; 43:1640–1644.
5. **Faiss S, Scherubl H, Riecken EO, et al.** Drug therapy in metastatic neuroendocrine tumors of the gastroenteropancreatic system. Recent Results Cancer Res 1996; 142:193–207.
6. **Norton JA.** Neuroendocrine tumors of the pancreas and duodenum. Curr Probl Surg 1994; 31:138–139.
7. **Metz D, Benjamin S.** Islet cell carcinoma of the pancreas presenting as bleeding from isolated gastric varices. Report of a case and review of the literature. Dig Dis Sci 1991; 36:241–244.
8. **Oberg K, Eriksson B, Janson E.** Interferons alone or in combination with chemotherapy or other biologicals in the treatment of neuroendocrine gut and pancreatic tumors. Digestion 1994; 55(Suppl 3):64–69.
9. **Modlin I, Lewis J, Ahlman H, et al.** Management of unresectable malignant endocrine tumors of the pancreas. Surg Gynecol Obstet 1993; 176:507–518.
10. **Zimmer T, Ziegler K, Bader M, et al.** Localization of neuroendocrine tumours of the upper gastrointestinal tract. Gut 1994; 35:471–475.
11. **Bader M, Koppenhagen K.** Somatostatin receptor scintigraphy in the diagnosis of neuroendocrine gastroenteropancreatic tumors. Recent Results Cancer Res 1996; 142:137–162.

ADDRESS: *Darwin L. Conwell, MD, Department of Gastroenterology, S40, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195.*