Heterotopic pancreas is a relatively infrequent lesion most often found in the stomach. Four histologic types are recognized: total, canalicular, exocrine, and endocrine heterotopia. To our knowledge, only 2 cases of purely endocrine heterotopic pancreas have been reported in detail. We describe the case of a patient with gastric and duodenal ulcers and gastric endocrine heterotopia. The lack of mass formation, histomorphology, and immunohistochemical features simulating islets of Langerhans supported the diagnosis. We conclude that purely endocrine heterotopic pancreas is a very rare entity that, when present, can simulate a primary or metastatic neuroendocrine tumor. Adequate sampling of the specimen, histomorphologic pattern, and immunohistochemistry are important for the purpose of distinguishing between a neuroendocrine tumor and purely endocrine heterotopia.

**REPORT OF A CASE**

The patient was a 61-year-old white man with a long history of insulin-dependent diabetes mellitus and end-stage renal failure. He presented to the emergency room following several days of severe leg pain, for which he had taken analgesics without relief of his symptoms. While in the emergency room, he suffered an episode of heme-positive “coffee-ground” emesis, but refused nasogastric lavage. Other past medical history was significant for hypertension, chronic obstructive pulmonary disease, hemodialysis for the previous 5 years, a gastrointestinal bleed from a duodenal ulcer, and diverticulosis. Surgical history was notable for a right femoral pseudoaneurysm repair, left hip repair, and several right lower extremity digit amputations. He had a 30-pack-year smoking history, but had quit smoking 5 years prior to admission. Family history was noncontributory. Findings from the physical examination were unremarkable except for diminished right lower extremity pulses. Laboratory tests showed a white blood cell count of 20.45 µg/dL with a left shift and a serum urea nitrogen/creatinine level of 55/4.8 µg/dL. A chest radiograph showed bilateral pleural effusions and pulmonary edema. He was placed on dialysis, and blood cultures were drawn that later grew methicillin-resistant *Staphylococcus aureus*. The patient was administered antibiotics, and his glucose levels and hypertension were brought under control. Serial hematocrits were taken to monitor his gastrointestinal bleeding, as he continued to refuse a nasogastric tube. Several days later, he again suffered an episode of “coffee-ground” emesis and underwent an upper endoscopy, which showed esophagitis, gastritis, and a clean-based duodenal ulcer. One week later, he had a new onset of gastrointestinal bleeding and underwent a near-total gastrectomy and cholecystectomy. He remained in the intensive care unit following the surgery, and died 6 weeks later of sepsis.

**MATERIALS AND METHODS**

The surgical specimen was fixed in 10% buffered formalin, routinely processed, and embedded in paraffin. Three-micrometer-thick sections were cut and stained with hematoxylin-eosin, and immunohistochemical stains were performed as follows. The immunohistochemical stains were performed as follows. The slides were deparaffinized in xylene and hydrated in decreasing grades of ethanol. Endogenous peroxidase activity was blocked by immersing the slides in 6% hydrogen peroxide for 3 minutes. They were then washed in water and phosphate-buffered saline. The slides were then treated with normal horse serum for 5 minutes and incubated with the primary antibody for 30 minutes. Primary antibodies used, along with type, code, source, and working dilution, are specified in the Table. Slides were then incubated for 25 minutes with linking solution (LSAB Kit, Universal, K0690, Dako Corporation, Carpinteria, Calif) and for 25 minutes with streptavidin-peroxidase, using phosphate-buffered saline washings between steps. Diaminobenzidine (K3468, Dako) was the chromogen. Harris hematoxylin was the counterstain. The slides were then rinsed in tap water and dehydrated in increasing grades of isopropyl alcohol, cleared with xylene, and mounted using a synthetic neutral resin.
Sources of Primary Antibodies*

<table>
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<th>Primary Antibody</th>
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<th>Code No.</th>
<th>Source</th>
<th>Working Dilution</th>
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<td>A565</td>
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* M indicates monoclonal antibody; P, polyclonal antibody; and GRP, gastrin-releasing peptide.
† Dako Corporation, Carpinteria, Calif; Cambridge, Turnpike Billerica, Mass; Immunotech, Westbrook, Maine.

**PATHOLOGIC FINDINGS**

A previously opened stomach, portion of duodenum, and gallbladder were obtained. The stomach measured 16.5 cm along the lesser curvature, and 25 cm along the greater curvature. A 2.0-cm cuff of duodenum was present. Multiple gastric and 1 duodenal mucosal ulcerations were present, ranging from 3.0 to 0.4 cm in diameter. None of the ulcerations showed heaped-up edges, and 2 of the ulcers were present at both the gastric and duodenal specimen margins. No masses were identified. The gallbladder appeared grossly unremarkable.

Light microscopic examination showed benign ulcers. Additionally, multiple 0.1- to 0.4-mm nodules were dif-

**Figure 1.** Microscopic heterotopic nodules were diffusely scattered within the submucosa (a) and muscularis propria (b) (hematoxylin-eosin, original magnification ×20).

**Figure 2.** The immunostain for chromogranin was strongly positive (hematoxylin-eosin, original magnification ×60 [a]; chromogranin, original magnification ×60 [b]).
fusely scattered within the submucosa and muscularis propria of the gastric wall (Figure 1), but were absent in the duodenum. They were composed of small, bland epithelial cells arranged in well-circumscribed, solid nests without vascular pseudorosettes and resembled normal pancreatic islets. Some of the nodules were located in the submucosa beneath areas of mucosal ulceration, but did not show communication with or disruption of the mucosa. No stromal reaction was identified. Immunohistochemistry showed the nodules to be strongly positive for chromogranin (Figure 2), with focal positivity for insulin and somatostatin (Figure 3) following a physiologic staining pattern. Stains for glucagon, gastrin-releasing peptide, and gastrin were negative. Neither mitoses nor necrosis was identified. Therefore, histologically and immunophenotypically these nodules were considered to be an incidental finding of gastric endocrine pancreatic heterotopia.

COMMENT

Heterotopic pancreas is a relatively infrequent lesion. It is considered to arise during embryologic development of the gastrointestinal tract. The normal pancreas is derived from several evaginations of the wall of primitive duodenum. The dorsal diverticulum becomes the body and tail, and the ventral diverticulum becomes the head. The 2 parts fuse at the sixth week of gestation. If 1 or more evaginations remain in the wall of the bowel, it may be carried longitudinally either proximally or distally from the remainder of the gland by the growing gastrointestinal tract.

The largest series of heterotopic pancreas were reported by Dolan et al, Lai and Tompkins, and Armstrong et al, who studied 212, 37, and 34 cases, respectively. Multiple isolated cases of pancreatic heterotopia have also been described. To our knowledge, only 2 cases of purely endocrine heterotopic pancreas have been reported in detail. Although the vast majority of patients are asymptomatic, heterotopic pancreas is important to be recognized clinically because of its possible association with symptoms. Gastric pain is most commonly reported, and patients may also complain of bleeding, nausea, vomiting, and chest pain. The mechanism for the production of symptoms is unclear. Armstrong et al found a correlation between the presence of symptoms, size of the lesion (greater than 1.5 cm), and extent of mucosal involvement. However, all cases in this series showed exocrine differentiation. When there is ulceration of the overlying mucosal surface, the associated bleeding is easily explained. In the absence of mucosal involvement, a cause is less certain. The patients in the 2 reported cases of purely endocrine heterotopia presented clinically with melena and were found to have ulcerated gastric polypoid projections of ectopic endocrine pancreas. In our case, there was an absence of exocrine tissue or causative hormone production, as well as a lack of significant size or mass formation to disrupt the mucosa. Therefore, the cause-effect relationship between the ectopic pancreas and the ulceration and bleeding of the patient described herein is uncertain.

Purely endocrine heterotopic pancreas may mimic a neuroendocrine tumor. The histologic appearance may be similar. Both have monomorphous, medium-sized cells that may be arranged in microlobules. Neuroendocrine tumors, however, usually form a solid tumor mass that may be arranged in trabeculae, pseudovascular rosettes, tubules, or solid sheets. The endocrine cells in our case formed well-circumscribed microscopic nests that were diffusely distributed in the submucosa and muscularis propria of the gastric wall without forming a mass. Although a primary endocrine neoplasm was excluded, the remote possibility of a metastatic endocrine neoplasm was considered. The scattered nature of the lesion, the small size of the nests, and the lack of stromal reaction strongly favored endocrine pancreatic heterotopia. Immunohistochemical characterization of the cells helped confirm the histologic impression. The nodules were strongly positive for chromogranin. A large percentage of the cells expressed insulin, mainly in the central portion of the nodules, while fewer cells showed somatostatin positivity in...
the periphery.8 The cytologic distribution and percentages were similar to those of the normal islets of Langerhans. The immunohistochemical findings thereby supported the histologic impression of purely endocrine heterotopic pancreas.

We conclude that purely endocrine heterotopic pancreas is a very rare entity that, when present, can simulate a primary or metastatic neuroendocrine tumor. Adequate sampling of the specimen, histomorphologic pattern, and immunohistochemistry are important for the purpose of distinguishing between a neuroendocrine tumor and purely endocrine pancreatic heterotopia.

We thank Mehrdad Nadji, MD, for his critical review of this manuscript.

References