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Islet cell neoplasia is a frequent occurrence in multiple endocrine neoplasia type 1 (MEN 1). Sixteen of 27 patients with MEN 1 developed functioning endocrine pancreatic tumor syndromes. Eleven of the 16 developed Zollinger-Ellison syndrome and each was evaluated by a combination of computed tomography and hepatic angiography to exclude hepatic metastasis and percutaneous transhepatic catheterization to localize the tumor. Seven of the 11 patients were found to have duodenal gastrinomas with multiple duodenal tumors in three patients. Four of the 11 patients had only pancreatic gastrinomas. In addition to the gastrinomas, other types of islet tumors in the pancreatic body or tail were found in nine of the 11 patients. None of the patients had hepatic metastases. Seven of the 11 patients were treated by distal pancreatectomy and since 1986 all patients have had duodenotomies as part of the surgical exploration. Postsurgical evaluation ranging from three months to 14 years indicates that 10 of 11 patients have normal basal gastrin levels. We conclude that duodenal gastrinomas are common in MEN 1 and can be managed successfully by appropriate operative intervention. (Henry Ford Hosp Med J 1992;40:195-8)

Multiple endocrine neoplasia type 1 (MEN 1) is characterized by hyperplasia and neoplasms of the pituitary, parathyroids, and pancreatic islets. Hyperparathyroidism (HPT) occurs in more than 90% of patients and endocrine pancreatic tumors in 60% (nearly all of whom have HPT as well). Approximately 40% of patients develop pituitary adenomas, most of which secrete prolactin (1). In addition to the three principle organs involved, some of these patients develop adrenal cortical tumors, bronchial carcinoids, and thymic carcinoids (2). The latter are usually malignant whereas the adrenal cortical tumors are usually benign. In some families, subcutaneous lipomas are frequent and may require surgical treatment.

Our approach to the diagnosis of MEN 1 patients at the University of Michigan is to screen carefully for all components of the syndrome in family members of those suspected of having the syndrome after detection of a functioning islet-cell tumor syndrome or primary HPT due to hyperplasia, particularly when the individual glands are asymmetrically involved (1). During the 15-year interval from 1976 to 1991, 27 patients with the MEN 1 syndrome were identified. Of these, 16 were determined to have functioning endocrine pancreatic tumor syndromes. During the 15-year period, 11 patients in this group proven to have the Zollinger-Ellison syndrome (ZES) were selected for surgical treatment with the goal of excising their tumor(s) and any lymphatic metastases present. The purpose of this paper is to describe the surgical management of these patients and the results of their treatment.

Methods

The 11 patients with ZES were all proven to have the MEN 1 syndrome on the basis of family history and/or previous or concomitant HPT and/or pituitary adenomas. The mean age of these patients was 39 years at the time of treatment. There were seven females and four males. All 11 patients had HPT. Nine had parathyroidectomies before surgical treatment of their ZES (2-9 years) and two underwent parathyroidectomy at the same time as their abdominal procedures. Seven of the 11 patients had pituitary adenomas, all of which secreted prolactin. Two patients with Cushing's syndrome had unilateral functioning adrenal cortical adenomas. All 11 patients had intact stomachs at the time of surgical treatment.

Since 1978, after ruling out hepatic metastases (computed tomography and selective angiography), patients with MEN 1 ZES were selected for operation by percutaneous transhepatic selective venous sampling (TVS) for gastrin. Regional localization of an elevated gastrin level was noted in each patient selected for operation (3,4).

Islet cell tumors in the head or uncinate process were enucleated after exploration of the entire pancreas and palpation of the duodenum. Seven of the 11 underwent distal pancreatectomies regardless of the findings in the head or duodenum. Four patients had tumors excised from the duodenum and/or pancreas without a distal pancreatectomy. Since 1986, all patients had duodenotomies as part of their exploration. Patients with duodenal tumors had regional dissections of periduodenal and peripancreatic lymph nodes.

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Table 1
Location of Gastrinomas in MEN 1 ZES Patients

Gastrinoma Location	Number of Patients
Pancreas	7/11 (64%)
Pancreas only	4/11 (36%)
Duodenum	7/11 (64%)
Duodenum only	4/11 (36%)
Duodenum and pancreas	3/11 (27%)
Multiple gastrinomas in duodenum	3/11 (27%)
Other gross neuroendocrine tumors in pancreas*	11/11 (100%)

*Found in 9 of 11 at initial exploration.

Results

Gastrinomas were found in the pancreas in seven of 11 patients (64%). In three of these patients, additional gastrinomas were found in the duodenum. Altogether, seven of 11 patients had duodenal gastrinomas (64%). In three of the seven with duodenal gastrinomas, the tumors were multiple. Only 36% of patients had gastrinomas only in the pancreas. However, grossly apparent tumor(s) were found in the pancreatic body or tail in nine of 11 (82%). Most of these tumors stained negative for gastrin. All gastrinomas were verified by positive immunohistological study (Table 1).

None of the patients had liver metastases. Six (55%) patients had metastatic lymph nodes. Five of seven (71%) with duodenal gastrinomas were proven to have metastatic lymph node involvement. One patient with a small concomitant neuroectodermal (NE) tumor of the body (somatostatinoma) had one node staining positive only for somatostatin. This was the only patient who had a concomitant malignant pancreatic NE tumor (Table 2).

In the pancreas of seven patients who had initial distal pancreatectomies, one or more NE tumors were found in each. None of these patients has developed a recurrent NE tumor. A distal pancreatectomy was not performed in four patients, three of whom developed recurrent hormonal syndromes. Two patients required a distal pancreatectomy for a gastrinoma in the body. Early in this experience, two patients had concomitant total gastrectomies and two had vagotomies and pyloroplasties. The remaining seven patients have intact stomachs with vagal innervation. Thus, nine of the 11 patients still have intact stomachs.

After periods ranging from three months to 14 years, 10 of 11 (91%) patients have normal basal gastrin levels. Currently, three of 11 have negative secretin stimulation tests and can be categorized as biochemical as well as clinical "cures." One patient, who underwent a distal pancreatectomy for an 8 cm gastrinoma in 1977, died in 1991 from chronic heart disease. Her basal serum gastrin levels and secretin stimulated gastrin levels remained normal throughout her follow-up period.

Although the other seven patients with normal basal gastrin levels have positive secretin tests, they are clinically free of symptoms and have required no drug therapy for periods ranging from three months to 13 years. Two patients required reoperation for hyperinsulinoma but had no evidence of recurrent gastrinoma. One patient, who required a reoperation for a second gastrinoma seven years after resection of a primary gastrinoma in the pancreatic body, currently has a negative secretin study six months following the second operation. One patient with three primary duodenal gastrinomas and one in the pancreatic neck associated with large peripancreatic lymph node metastases has a persistently elevated basal gastrin level (300 to 500 pg/mL) and requires omeprazole to remain free of symptoms.

Table 2
Malignant Gastrinomas in MEN 1 ZES Patients

Type	Number of Patients
Malignant duodenal gastrinomas	5/7 (71%)
Malignant pancreatic gastrinomas	0/4 (0%)
Malignant NE tumor of pancreas	1/11 (9%)
Metastatic lymph nodes	6/11 (55%)
Liver metastases	0/11 (0%)

Discussion

The most frequent clinical manifestation of MEN 1 pancreatic involvement is ZES, usually developing during the third or fourth decade of life but often not diagnosed or treated until after a number of symptomatic years despite the fact that most of these patients have had HPT treated surgically at an earlier age (1-6). Insulinomas are the second most common functional tumors in MEN 1 patients and may develop at any age. Although 30% of all ZES patients are found to have the MEN 1 syndrome, the great majority of insulinomas are sporadic and only about 4% to 5% are determined to be MEN 1. Additional pancreatic tumors found in MEN 1 patients are VIPomas, glucagonomas, somatostatinomas, and polypeptidomas (PPomas) (1). In some MEN 1 patients, tumors may develop and metastasize to lymph nodes or the liver without any clinical manifestations whatsoever. Occasionally more than one functional hormone syndrome may develop in the same MEN 1 patient. Most often this occurs asynchronously as was the case in two of the patients in this series. Most patients with pancreatic disease requiring surgical intervention present with a single syndrome caused by hypersecretion of a specific hormone. However, in some patients, a tumor may be detected by an imaging study obtained only after screening studies have shown an elevation of one or more hormones such as pancreatic polypeptides or somatostatin.

The surgical treatment of MEN 1 pancreatic disease is controversial (7-12). One of the major issues centers around the fact that virtually all patients with MEN 1 pancreatic disease have a diffuse islet-cell hyperplasia expressed as nesidioblastosis, islet-cell hyperplasia, microadenomatosis, and/or benign or malignant islet-cell tumors (13). As a result, some have concluded that a true cure of the pancreatic disease can only be achieved by total pancreatectomy. Furthermore, the malignant potential of MEN 1 islet-cell neoplasms has been considered relatively low. Nevertheless, there is accumulating evidence that the majority of gastrinomas in MEN 1 patients are in fact malignant and that lymph node and/or hepatic metastases will develop in most pa-

tients with ZES if followed for a long enough period (6). Other functional and silent NE neoplasms in these patients also have malignant potential. Patients with ZES pose a special problem because the gastrinomas are often small, multiple, found in both duodenum and pancreas, and associated with other NE tumors (5). Because surgical attempts to control hypergastrinemia have frequently failed in the past, many surgeons have recommended only medical therapy until or unless a tumor has been imaged by computed tomography or other studies (9-12,14-18). Even in these cases, failure is likely because the imaged tumor excised is often not a gastrinoma. It has been our contention that many of these patients could be successfully treated surgically, providing all tumors secreting gastrin could be found and excised with any metastatic lymph nodes involved (7,8). This opinion was based on the fact that in previous immunohistological studies of MEN 1 pancreases, we found that only discrete tumors stained positive for gastrin and that the more diffusely involved islets and pancreatic microadenomas were consistently negative for gastrin (13).

After ruling out hepatic metastases in MEN 1 ZES patients, it has been our policy to perform TVS for gastrin and to explore those patients demonstrating regionalized, rather than diffuse, secretion of gastrin as determined by these studies (3,8). Most patients were found to have gastrinomas in the head or duodenal region although several have had primary gastrinomas in the body or tail with or without other gastrinomas in the duodenum. Because the duodenum is such a common site for gastrinomas in MEN 1 patients, we began to perform a duodenotomy routinely in all patients after 1986. The entire duodenal mucosa must be carefully evaluated by eversion and gentle palpation because these tumors may be as small as 1 mm and are often multiple in MEN 1 patients (19,20). Furthermore, even these very small tumors may be malignant and have already metastasized to contiguous lymph nodes. As a result, routine periduodenal and peripancreatic lymph node dissection is essential whenever a duodenal gastrinoma is found, regardless of size. Five of seven (71%) patients with duodenal tumors in this series had metastatic nodal involvement. Duodenal gastrinomas less than 0.5 cm are usually not invasive and can be locally excised, whereas larger gastrinomas must be excised with a margin of full thickness duodenal wall. In a similar experience, Pipeleers-Marichal and colleagues (5) emphasized the importance of duodenal gastrinomas in MEN 1 patients. They found that 100% of eight MEN 1 patients had duodenal gastrinomas and in five cases these were multiple. There were regional lymph node metastases found in four of eight (50%) (5). In addition to excision of the duodenal disease, any palpable tumors in the head or uncinate process should be enucleated. We have encountered no pancreatic gastrinomas that were locally invasive and could not be excised with techniques similar to those used to remove benign insulinomas of the head. For the past decade we have, with few exceptions, also performed a distal pancreatic resection even when no palpable tumors have been identified. In the four patients in which the body and tail were not resected, three developed recurrent disease; two multiple insulinomas and one a new gastrinoma. The fourth patient had a single NE tumor excised from the tail of the pancreas at the time of exploration following excision of three gastrinomas from the duodenum, two from the pancreatic head, and several metastatic peripancreatic lymph nodes. This patient remains eugastrinemic and has a negative secretin study three years after this operation. The other three patients have subsequently undergone reoperation distal pancreatectomies, achieving a "cure" of their syndromes. As a result, all 11 MEN 1 patients have been found to have grossly palpable tumors in their distal pancreas during the course of their disease. Currently, our distal resection is from the superior mesenteric vein, usually preserving the spleen by careful ligation of the small vessels from the splenic artery and vein.

The results in this series are contrary to those reports by others in which no patient's serum gastrin levels were normalized (10-12,14,16,18). All but one of our patients currently has a normal basal gastrin level and three have negative secretin tests. One of the latter developed recurrence of hypergastrinemia seven years after having tests. One of the latter developed recurrence of hypergastrinemia seven years after having normal basal levels but consistently positive secretin studies. At a second operation, a gastrinoma was found at the junction of the pancreatic neck and body. Three patients in the positive secretin group but with normal basal gastrin levels developed elevations of serum gastrin from one to six years after being eugastrinemic, concurrent with the development of recurrent HPT and hypercalcemia. In each, the basal serum gastrin level returned to normal after successful reoperations for HPT. Only the one patient with persistent hypergastrinemia has required other than short-term drug therapy for symptomatic hyperacidity during the time of this study. Similar results were recently reported by Pipeleers-Marichal et al (5). In their series of six MEN 1 patients who underwent surgical exploration and excision of duodenal gastrinomas, four were eugastrinemic at the time of follow-up.

Our results with an aggressive surgical approach to the MEN 1 ZES patient suggest that all patients should be explored if the liver is free of metastases, with the intent of performing a distal pancreatectomy, duodenal exploration, enucleation of any tumors in the head, and a peripancreatic lymph node dissection. Thus far, all of our patients have had discrete gastrinomas rather than diffuse hyperplasia or microadenomatosis as the source of their gastrin hypersecretion. Furthermore, the incidence of malignancy has been found to be similar to that in patients with sporadic ZES (60%), although fewer patients have had liver metastases. Although not yet proven with certainty, it appears that the biologic behavior of malignant duodenal gastrinomas which metastasize to lymph nodes is distinctly different from that of tumors which initially metastasize to the liver. Despite the presence of lymph node metastases, if the primary tumor and all nodes are excised, most of these patients may be cured of their disease (21-23). Curative resection appears to be possible in the former group whether they are sporadic or MEN 1 patients with gastrinomas.

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