TREATMENT INSULINOMA

Medical treatment, which consists of frequent carbohydrate meals and diazoxide or octreotide, is not always successful, and surgery is the optimal treatment. Surgical treatment, which ranges from enucleation of a single tumor to a distal pancreatectomy or partial pancreatectomy, has been curative in many patients. Chemotherapy may include streptozotocin, 5-fluorouracil, and doxorubicin. Hepatic artery embolization has been used for metastatic disease.

Glucagonoma These glucagon-secreting pancreatic NETs occur in <3% of patients with MEN 1. The characteristic clinical manifestations of a skin rash (necrolytic migratory erythema), weight loss, anemia, and stomatitis may be absent. The tumor may have been detected in an asymptomatic patient with MEN 1 undergoing pancreatic imaging or by the finding of glucose intolerence and hyperglucagonemia.

TREATMENT GLUCAGONOMA

Surgical removal of the glucagonoma is the treatment of choice. However, treatment may be difficult because approximately 50–80% of patients have metastases at the time of diagnosis. Medical treatment with somatostatin analogues (e.g., octreotide or lanreotide) or chemotherapy with streptozotocin and 5-fluorouracil has been successful in some patients, and hepatic artery embolization has been used to treat metastatic disease.

Vasoactive Intestinal Peptide (VIP) Tumors (VIPomas) VIPomas have been reported in only a few patients with MEN 1. This clinical syndrome is characterized by watery diarrhea, hypokalemia, and achlorhydria and is also referred to as the Verner-Morrison syndrome, the WDHA (watery diarrhea, hypokalemia, and achlorhydria) syndrome, or the VIPoma syndrome. The diagnosis is established by excluding laxative and diuretic abuse, by confirming a stool volume in excess of 0.5–1.0 L/d during a fast, and by documenting a markedly increased plasma VIP concentration.

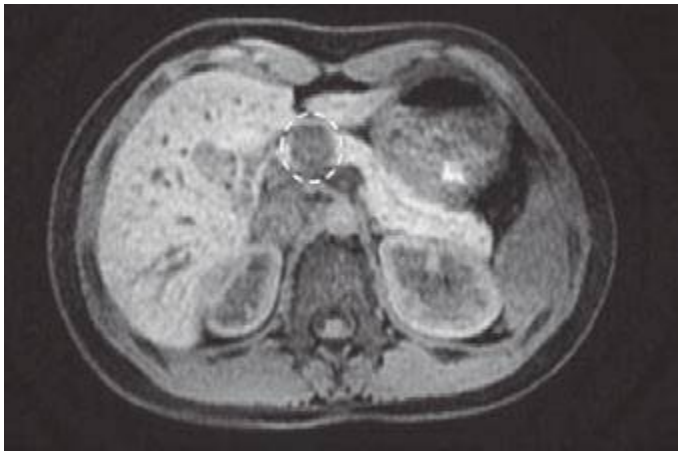
TREATMENT VIPOMAS

Surgical management of VIPomas, which are mostly located in the tail of the pancreas, can be curative. However, in patients with unresectable tumor, somatostatin analogues, such as octreotide and lanreotide, may be effective. Streptozotocin with 5-fluorouracil may be beneficial, along with hepatic artery embolization for the treatment of metastases.

Pancreatic Polypeptide-Secreting Tumors (Ppomas) and Nonfunctioning Pancreatic NETs PPomas are found in a large number of patients with MEN 1. No pathologic sequelae of excessive polypeptide (PP) secretion are apparent, and the clinical significance of PP is unknown. Many PPomas may have been unrecognized or classified as nonfunctioning pancreatic NETs, which likely represent the most common enteropancreatic NET associated with MEN 1 (Fig. 408-1). The absence of both a clinical syndrome and specific biochemical abnormalities may result in a delayed diagnosis of nonfunctioning pancreatic NETs, which are associated with a worse prognosis than other functioning tumors, including insulinoma and gastrinoma. The optimum screening method and its timing interval for nonfunctioning pancreatic NETs remain to be established. At present, endoscopic ultrasound likely represents the most sensitive method of detecting small pancreatic tumors, but somatostatin receptor scintography is the most reliable method for detecting metastatic disease (Table 408-3).

TREATMENT PPOMAS AND NONFUNCTIONING PANCREATIC NETS

The management of nonfunctioning pancreatic NETs in the asymptomatic patient is controversial. One recommendation is to undertake surgery irrespective of tumor size after biochemical assessment is complete. Alternatively, other experts recommend surgery based on tumor size, using either >1 cm or >3 cm at different centers. Pancreatoduodenal surgery is successful in removing the tumors in 80% of patients, but more than 40% of patients develop complications, including diabetes mellitus, frequent steatorrhea, early and late dumping syndromes, and other gastrointestinal symptoms. However, ~50–60% of patients treated surgically survive >5 years. When considering these recommendations, it is important to consider that occult metastatic disease (e.g., tumors not detected by imaging investigations) is likely to be present in a substantial proportion of these patients at the time of presentation. Inhibitors of tyrosine kinase receptors (TKRs) and of the mammalian



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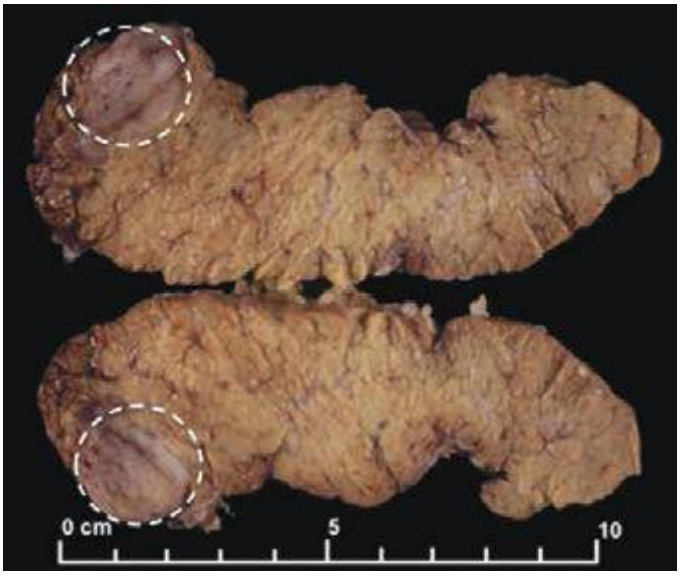

B

FIGURE 408-1 Pancreatic nonfunctioning neuroendocrine tumor (NET) in a 14-year-old patient with multiple endocrine neoplasia type 1 (MEN 1). *A.* An abdominal magnetic resonance imaging scan revealed a low-intensity >2.0 cm (anteroposterior maximal diameter) tumor within the neck of pancreas. There was no evidence of invasion of adjacent structures or metastases. The tumor is indicated by *white dashed circle*. ***B.*** The pancreatic NET was removed by surgery, and macroscopic examination confirmed the location of the tumor (*white dashed circles*) in the neck of the pancreas. Immunohistochemistry showed the tumor to immunostain for chromogranin A, but not gastrointestinal peptides or menin, thereby confirming that it was a nonsecreting NET due to loss of menin expression. *(Part A adapted with permission from PJ Newey et al: J Clin Endocrinol Metab 10:3640, 2009.)*