CHAPTER 51

Miscellaneous Tumors of the Pancreas

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Endocrine tumors of the pancreas are rare. Gastrinomas and insulinomas are the most common, occurring with an annual incidence of one per million. Other types have an annual incidence of less than one per 10 million.

Up to 50% of tumors are not associated with an identifiable hormonal syndrome and so are classified as non-functioning, although they often stain for classical peptide hormones (1). The remainder of the tumors are classified according to the secretory product responsible for the associated clinical syndrome. Tumor products may be entopic hormones (insulin, glucagon, somatostatin, and pancreatic polypeptide) or ectopic hormones (e.g., vasoactive intestinal peptide [VIP], gastrin).

Endocrine tumors of the pancreas are associated with the autosomal dominant syndrome, multiple endocrine neoplasia type 1 (MEN 1) (2) in about 25% of cases. The other features of the syndrome are parathyroid hyperplasia or adenomata and, in some cases, pituitary adenomas.

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COMMON BIOLOGICAL CHARACTERISTICS

Multiple Peptide Production

Pancreatic endocrine tumors are multipotential with respect to peptide production (3), and so they may produce other hormones during the course of the disease, giving rise to secondary hormone syndromes if secreted in sufficient amounts. In our series hormones other than those causing the primary syndrome became elevated in 7% of all cases, the most common secondary syndrome being caused by gastrin (4).

Tumors can stain for a variety of peptides by immunocytochemistry, and nearly 100% of islet cell tumors contain extractable pancreatic polypeptide (PP) (5), which is colocalized with other tumor products in secretory granules (6). As a result, up to 75% of tumors are associated with elevated levels of PP, but this does not produce a recognized clinical syndrome (7). Similarly 10% of VIPomas are associated with elevated levels of neurotensin (8).

Coproduction of peptides in the same precursor molecule can result in multiple peptide production. In the VIPoma syndrome, levels of peptide histidine methionine (PHM), a flanking peptide of VIP in the precursor molecule pre-pro-VIP, are invariably elevated, often to a greater extent than is VIP, because of its greater stability.
PHM may be responsible for some of the features of the syndrome (9). Similarly, elevated levels of the flanking glucagon-like peptides (GLP) 1 and 2 may be found in the glucagonoma syndrome (10).

Multiple tumors may be responsible for multiple peptide production (11). In MEN 1, patients often have multiple pancreatic and duodenal microadenomas producing a variety of hormones (12).

Molecular Heterogeneity

Post-translational enzymatic modification of precursor molecules may be altered in tumor cells, so that a variety of molecular weight forms of the secreted peptide may be released systemically (Fig. 1) (13). Some forms may be detected by radioimmunoassay but lack biological activity. Others may result in unusual features of the hormonal syndrome: Large molecular weight forms of glucagon may be responsible for villous hypertrophy and delayed gastric transit time (14), while large forms of somatostatin may paradoxically lead to hypoglycemia, by inhibition of counterregulatory hormones, rather than the hyperglycemia usually associated with the somatostatinoma syndrome (15). In one study only 26% of immunoreactive glucagon was biologically active (16). The proportion of different molecular weight forms may change, altering the clinical features, and gel chromatography may be useful in monitoring such changes.

Response to Stimulatory and Inhibitory Factors

Despite their apparently autonomous peptide production, pancreatic endocrine tumors remain responsive to exogenous factors. Stimulatory responses have formed the basis of dynamic diagnostic tests for the various syndromes, such as the tolbutamide test for both glucagonomas and somatostatinomas (15), but in our experience these investigations are rarely necessary.

The presence of receptors for somatostatin on the majority of pancreatic endocrine tumors is of much greater clinical significance. Somatostatin reduces plasma concentrations and inhibits the peripheral actions of many of the peptides released by these tumors (17). These features have been exploited for both therapeutic and imaging purposes by the development of the long-acting somatostatin analogue octreotide (18).

Low-grade Malignancy

Seventy percent of sporadic pancreatic endocrine tumors are malignant, with metastases occurring in the liver and local lymph nodes and rarely in bone or lungs, the latter carrying a very poor prognosis. Insulinomas are the exception, 90% being benign. However the malignant tumors are usually slow growing, with morbidity and early mortality resulting from hormone excess, and tumor bulk only presenting problems late in the disease. If tumors are nonfunctioning or symptoms of hormone excess are mild and nonspecific, there may be a considerable delay in diagnosis, perhaps in excess of 25 years in some cases of the somatostatinoma syndrome. In one series the median age at diagnosis was 53 years, with a delay of 35 months from the onset of symptoms, and the median survival was 5.8 years. Patients with MEN 1 are usually diagnosed at a younger age after less delay follow-

FIG. 1. Changes in circulating forms of somatostatin secreted by a neuroendocrine tumor following a test meal.
ing the onset of symptoms, and only 45% of them have malignant tumors. Their median survival is about 15 years (2).

Genetic Basis

The genetic abnormality responsible for the majority of sporadic pancreatic endocrine tumors is unknown. In MEN 1 there is an allelic deletion on chromosome 11 in the q13 region (19). This allele loss has also been demonstrated in a number of sporadic insulinomas (20).

CLINICAL SYNDROMES

The different peptide products of pancreatic endocrine tumors give rise to characteristic syndromes, which give rise to clinical suspicion. The diagnosis is then confirmed by radioimmunoassay demonstrating high circulating levels of the peptide associated with that syndrome. Peptide levels may be raised in association with other conditions (Table 1), but the elevation is rarely as marked, and the clinical syndrome is not apparent.

VIPoma Syndrome

The VIPoma syndrome results from the secretion of VIP and PHM by neuroendocrine tumors. In addition 75% of tumors secrete PP (7), and 10% secrete neuropeptide (8); however, there is no convincing evidence that these contribute to the clinical syndrome. In adults the tumors almost invariably arise from the pancreas; but about 10% of VIP-secreting tumors are ganglioneuromas, ganglioneuroblastomas, or neuroblastomas, and these usually occur in children (21). Fifty percent of patients have malignant disease, with gross metastases at the time of diagnosis (22).

The annual incidence of VIPomas is one per 10 million. The syndrome has various synonyms: Verner-Morrison syndrome, after the authors who first described it (23); watery diarrhea, hypokalemic, and achlorhydria (WDHA) syndrome, describing the major clinical features (24); and pancreatic cholera syndrome. The syndrome is characterized by profuse secretory diarrhea, without steatorrhea (25). Stool volumes of greater than 20 liters have been described, and most patients secrete more than 3 liters daily. This leads to profound dehydration, weakness, and lethargy, which is aggravated by hypokalemic acidosis, a consequence of potassium and bicarbonate loss in the stool (26). A plasma potassium as low as 2 mmol/L and pH of less than 7.1 are not uncommon. The diarrhea is initially intermittent but, when severe, may precipitate cardiovascular collapse and even death.

Other features of the syndrome are achlorhydria in 30% of cases; glucose intolerance caused by the glucagon-like actions of VIP in up to 50% of cases; hypercalcemia and hypophosphatemia, probably due to secretion of parathyroid hormone-related protein (PTHrP), in up to 75% of cases; flushing of the head and neck in 20% of cases; abdominal colic and weight loss, which may be profound in advanced cases; and, rarely, tetany, caused by hypomagnesemia (27).

Glucagonoma Syndrome

Pancreatic endocrine tumors secreting glucagon produce a characteristic, but largely unexplained, clinical syndrome. The annual incidence of the syndrome is estimated to be one per 20 million (28). There have been only two reported cases of extrapancreatic tumors secreting glucagon, one duodenal (29) and one renal (30). At least 75% of tumors are malignant, 50% of patients having gross metastases at the time of diagnosis (31).

The cardinal feature of the syndrome is the rash, necrotic migratory erythema (Fig. 2), which occurs in about 90% of cases (32). It usually starts in the groin, and migrates to the thighs, buttocks, perineum, and distal extremities. Erythematous blots are the initial manifestation, followed by scaling. Lesions become raised with vesicopustules and bullae and may become confluent. Erosion and crusting occurs followed by centrifugal clearing and then healing, which leaves indurated,
hyperpigmented areas. Histology of the rash reflects the stage of development of the lesion (33). It may be associated with angular stomatitis, cheilitis, atrophic glossitis, alopecia, onycholysis, vulvovaginitis, and urethritis. The etiology of the rash remains unclear, but it may be the result of a direct action of glucagon on the skin or on prostaglandins in the skin (34), hypoaminoacidemia (35), or zinc deficiency, since the rash resembles acrodermatitis enteropathica (36), which is pathognomonic of zinc deficiency, and since necrotic migratory erythema responds to zinc therapy despite normal circulating levels.

Other clinical features include impaired glucose tolerance in almost all cases and sometimes mild diabetes; weight loss owing to the catabolic effects of glucagon, which can be severe enough to be fatal; normochromic, normocytic anemia; severe depression or other psychiatric disturbance; altered bowel habit, usually constipation; and severe life-threatening venous thrombosis (33).

The characteristic triad of diabetes (caused by inhibition of insulin secretion), cholelithiasis (caused by inhibition of gallbladder contraction), and steatorrhea (caused by inhibition of pancreatic and gallbladder secretions) (39), is seen in about 90% of patients with pancreatic somatostatinomas. The diabetes is usually mild, but there have been reports of patients presenting with diabetic ketoacidosis (40,41). Hypoglycemic episodes have been described in a few patients, possibly as a result of high levels of large molecular weight somatostatin. These may coexist with diabetes (15). Other features of the syndrome include postprandial fullness, weight loss, and anemia.

Patients with duodenal tumors may present with jaundice or pancreatitis, owing to ampullary obstruction, or intestinal obstruction or hemorrhage.

Other Pancreatic Endocrine Tumors

PP is frequently secreted in large quantities by pancreatic endocrine tumors. This is not surprising since PP cells constitute 10% of the islet population. Seventy-five percent of nonfunctioning tumors are associated with elevated levels of PP, and in the majority of these tumors there is PP cell hyperplasia. However, although PP was initially thought to be a mediator of a watery diarrhea syndrome, there is no clinical syndrome associated with pure PPomas (7).

Ten percent of VIPomas secrete neurotensin, and occasionally neurotensin is produced by other tumors or by a pure neurotensinoma (8). There have been no consistent features associated with neurotensin secretion from pancreatic endocrine tumors, although one report suggested it had been responsible for cyanosis and edema in a patient with a VIPoma (42).

There have been several reports of pancreatic endocrine tumors secreting growth hormone-releasing hormone, leading to gigantism or acromegaly as a result of somatotroph hyperplasia or adenoma (43), adrenocorticotropic hormone producing Cushing’s syndrome (44,45), and, in one case, growth hormone producing acromegaly (46).

Hypercalcemia as a result of PTHrP secreted by pancreatic neuroendocrine tumors has been reported in a number of cases, with no associated hormonal syndrome (47,48). However it is probable that the hypercalcemia associated with the VIPoma syndrome is usually mediated by this peptide.

Serotonin-secreting tumors of the pancreas are extremely rare, but the associated carcinoid syndrome is similar to that caused by midgut carcinoid tumors, with flushing and diarrhea.

Several other peptide hormones may be secreted by pancreatic endocrine tumors, including neuropeptide Y, neuromedin B, calcitonin gene-related peptide, bombe-
sin, and motilin; but these do not cause distinctive clinical syndromes.

Up to 50% of pancreatic endocrine tumors are nonfunctioning (1). These tumors may stain for classical pancreatic hormones but do not secrete hormone in sufficient quantities to produce a clinical syndrome. In the past such tumors have often been mistaken for pancreatic adenocarcinomas but are now increasingly recognized as histological techniques become more powerful. Patients commonly present with abdominal pain and weight loss but may have pancreatic (49), obstructive jaundice, or intestinal obstruction as the presenting feature. The prognosis is worse for this patient group (a 50% survival of less than 5 years) because there is a higher incidence of malignancy when pancreatic endocrine tumors are nonfunctioning, patients usually present at a more advanced stage, and tumors are less responsive to palliative therapy.

FIG. 4. Gastrointestinal arteriogram: blush of neuroendocrine tumor in pancreatic head (arrow).

TUMOR LOCALIZATION

Localization of pancreatic endocrine tumors can present a major challenge. Large tumors and hepatic metastases are easily visualized by ultrasonography and computed tomography (CT) scanning (Fig. 3). Vascular, gastrointestinal, somatostatinomas, and nonfunctioning tumors are usually greater than 2 cm in diameter, and over 50% will have metastasized by the time of diagnosis. However, small tumors, which account for the majority of gastrinomas and insulinomas, are best localized by a combination of ultrasonography, rapid, dynamic CT scanning following bolus injection of contrast, and meticulous highly selective angiography (Fig. 4) (30). In experienced centers, these techniques have a 70% specificity and 100% sensitivity (31). Intra-arterial dynamic CT scanning does not appear to enhance detection rate (32), but delayed scanning 4 to 6 hours after contrast administration may improve localization of small tumors (33). Transhepatic percutaneous portal venous sampling, with assay of the appropriate tumor product, does not usually give sufficient resolution to enhance peripancreatic localization (34,55), and is complicated by anomalous venous drainage and fluctuating tumor secretion.

Newer techniques such as endoscopic ultrasonography (36), spiral CT scanning, and radiolabeled somatostatin analogues (57) may improve detection rates but require further evaluation.

During surgery, intraoperative ultrasound (56) and endoscopic transillumination may successfully localize small tumors, particularly duodenal lesions in patients with MEN 1.

HISTOLOGIC FEATURES

The histologic features of pancreatic endocrine tumors are characteristic. On light microscopy, the solid
FIG. 5. Conventional histology (hematoxylin and eosin stain) of a pancreatic A cell (glucagon-producing) tumor.

FIG. 6. Low-power electron micrograph of a pancreatic A cell tumor with typical electron-dense granules (mean diameter 300 nm).
**FIG. 7.** A pancreatic A cell tumor showing dense immunoreactivity for glucagon. Peroxidase antiperoxidase stain with hematoxylin counterstain.

**FIG. 8.** A poorly granulated pancreatic VIP-producing tumor immunostained for chromogranin. Peroxidase antiperoxidase stain with hematoxylin counterstain.
trabecular or glandular pattern of the tumor can be identified (Fig. 5). One pattern usually predominates, although combinations can sometimes be found in different parts of the same tumor. On electron microscopy, secretory granules can be seen (Fig. 6). The appearance of the granules is usually characteristic of the peptide they contain and hence helps in the identification of the type of pancreatic endocrine tumor. Some tumors, however, contain cells that have atypical or a mixture of typical and atypical granules.

Immunocytochemical methods can be utilized (59), not only to identify the various hormones produced by these tumors by using antibodies against specific peptides (Fig. 7), but to assess their neuroendocrine nature by using stains for neuron-specific enolase (a cellular enzyme) (60) and chromogranins (specific granular proteins) (61) (Fig. 8). These methods are particularly useful in identifying nonfunctioning tumors. Immunocytochemistry often detects hormones in the tumor cells other than those circulating in the plasma and causing the clinical syndrome.

In situ hybridization, detecting hormone mRNA, can be used to assess hormone synthesis by tumor cells (62). This may demonstrate that cells that are poorly granulated are nonetheless very actively synthesizing.

TREATMENT

The therapeutic modalities available for the treatment of pancreatic endocrine tumors are surgery, cytotoxic chemotherapy, hepatic embolization, octreotide therapy, or medical treatment aimed at specific features of each syndrome. Surgery offers the only chance of cure, and the other treatment options are merely palliative. However, since the tumors are usually slow growing and early morbidity and even mortality result from hormone hypersecretion, palliative treatment to reduce tumor bulk and peptide secretion is very worthwhile. Such treatment is indicated when there is significant morbidity from hormonal syndromes or from tumor bulk encroaching on neighboring structures, but not in asymptomatic individuals. Hormone levels and circulating markers of pancreatic endocrine tumors, such as pancreatic polypeptide or GAWK (a fragment of chromogranin) (63), are useful for monitoring response to therapy.

Surgery

Complete surgical excision offers the only chance of cure for pancreatic endocrine tumors (64). Since the majority of tumors are malignant, with metastases present at the time of diagnosis, this is rarely feasible, although there are reports of cure by the enucleation of tumor deposits in the presence of metastatic disease (65). Non-curative tumor debulking can provide excellent palliation by reducing hormone levels and relieving morbidity from local effects.

There have now been a number of cases of hepatic transplantation for pancreatic endocrine tumors, when metastatic disease has been confined to the liver and the primary tumor has been localized and is resectable. The majority of patients are still alive, with a maximum disease-free survival of 3 years (66–68).

Cytotoxic Chemotherapy

A number of chemotherapeutic regimens have been advocated for the treatment of malignant pancreatic endocrine tumors. The most commonly used agent is streptozotocin, a nitrosourea with specific toxicity for islet cells. Streptozotocin alone has been reported to produce a biochemical response (hormone levels reduced by at least 50%) in 64% of patients and a tumor response (regression of tumor size by at least 50%) in 50% of patients (69). However, most studies have found a lower response rate but, by using a combination of streptozotocin and 5-fluorouracil, have achieved a good palliative response in up to 65% of cases, with a median duration of response of 17 months (70). We use a regimen of streptozotocin 500 mg/m² and 5-fluorouracil 400 mg/m² given by intravenous infusion on alternate days for 10 days. Four courses are given at 2 to 3 monthly intervals, and then the response to treatment is assessed before repeating the course. Renal, hepatic, and bone marrow function should be closely monitored for evidence of toxicity.

Dimethyltriazenoimidazole carboxamide (Dacarbazine, DTIC) has been reported to be particularly effective in the treatment of glucagonomas, with a biochemical response rate as high as 100% and a duration of response of over one year (71). Human leucocyte interferon has been advocated for the treatment of pancreatic endocrine tumors, particularly VIPomas, in which a biochemical and hormonal response rate of 100% has been reported, with a median duration of response of 8.5 months, in 7 patients (72). However VIPomas are notably sensitive to chemotherapy, streptozotocin and 5-fluorouracil producing a response in over 90% of patients, and interferon is associated with considerable morbidity. Other agents used include doxorubicin, vincristine, and tubercidin.

Hepatic Embolization

Hepatic metastases receive their blood supply solely from the hepatic artery, while the surrounding normal liver is also supplied by the portal vein (Fig. 9). Thus metastases can be selectively devascularized by embolization of the hepatic artery or its branches, and good
palliation can be achieved by the subsequent reduction in tumor bulk (73, 74). The procedure is obviously contraindicated if the portal vein is occluded. Other relative contraindications are replacement of 50% of the liver by tumor or significant derangement of liver function. A good response to embolization, with over 50% reduction in tumor bulk, occurs in about 60% of patients, and the procedure can be repeated when symptoms recur (75). Octreotide should be given to cover the embolization, as there can be massive hormone release from the necrotic metastases; and broad-spectrum antibiotic prophylaxis is recommended, although all patients will become pyrexial as a result of tumor necrosis.

**Octreotide**

Endogenous somatostatin is an inhibitor of multiple endocrine and gastrointestinal functions and, in particular, reduces secretion of peptides, both from normal and tumor cells, and blocks their peripheral actions. Unfortunately, continuous infusion is necessary for its therapeutic use because its half-life in plasma is only 3 minutes. However, octreotide, a long-acting analogue preserving the amino acid sequence responsible for somatostatin’s biological activity, was developed for therapeutic use (18). It is given subcutaneously, starting at doses as low as 50 μg twice daily. Up to 90% of patients with hormonal syndromes respond to octreotide, with a reduction in symptoms and decrease in hormone levels often occurring within 24 hours. It can be life-saving in a severe VIPoma crisis (76). However, no convincing evidence exists that octreotide decreases tumor bulk. There is usually a gradual loss of effectiveness, with increasing doses required, up to a maximum of 500 μg thrice daily. At this dose, symptoms usually recur after about 24 months and patients are then resistant to all treatment modalities. All 10 patients in one series died within 5 months (77).

**Other Medical Therapies**

In the glucagonoma syndrome, topical and oral zinc and a high-protein diet to correct the hypoaminoacidemia may lead to improvement of the rash. Amino acid infusions and blood transfusions have been advocated for acute exacerbations. Anticoagulation appears to have little effect on thrombotic disease, but aspirin or dipyridamole may be helpful. In both the glucagonoma and somatostatinoma syndromes, diabetes is usually mild, but occasionally insulin may be required.

A variety of agents have been used to treat the diarrhea of the VIPoma syndrome (78), of which prednisolone at doses of up to 80 mg daily appears to be the most effective, controlling symptoms for up to 6 months. These drugs have rarely been necessary, however, since the advent of octreotide therapy. Acute crisis in the VIPoma syndrome requires intensive fluid and electrolyte support, often with central venous pressure monitoring, to
correct fluid losses of up to 20 liters a day, potassium deficits of 300 mEq daily, and possibly magnesium deficiency.

CONCLUSIONS

The diagnosis of pancreatic endocrine tumors has benefited enormously from advances in radioimmunoassay and histochemistry, and new radiological techniques are contributing to improvements in localization. In most cases treatment can only be palliative, but the development of octreotide has led to a considerable reduction in the morbidity associated with these tumors. The low-grade malignancy of most tumors means that most patients now survive for several years after diagnosis with a minimum of symptoms.

REFERENCES

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