Pancreatic Neuroendocrine Tumors

The preferred term for tumors of the pancreatic islet cells ("islet cell tumors") is *pancreatic neuroendocrine tumors or PanNETs*. They are rare in comparison with tumors of the exocrine pancreas, accounting for only 2% of all pancreatic neoplasms. PanNETs can occur anywhere along the length of the pancreas, embedded in the substance of the pancreas or arising in the immediate peripancreatic tissues. They resemble their counterparts, carcinoid tumors, found elsewhere in the alimentary tract (Chapter 17). These tumors may be single or multiple and benign or malignant. Pancreatic endocrine neoplasms often elaborate pancreatic hormones, or may be nonfunctional.

Like other endocrine neoplasms, it is difficult to predict the behavior of a pancreatic endocrine neoplasm based on their light microscopic appearance. Unequivocal criteria for malignancy include metastases, vascular invasion, and local infiltration. The functional status of the tumor has some impact on prognosis, in that approximately 90% of insulin producing tumors are benign, while 60% to 90% of other functioning and nonfunctioning pancreatic endocrine neoplasms are malignant. Fortunately, insulinomas are the most common subtype of pancreatic endocrine neoplasms.

The genome of sporadic PanNETs recently has been sequenced, with identification of recurrent somatic alterations in three major genes or pathways:

- *MEN1*, which causes familial MEN syndrome, type 1, also is mutated in a number of sporadic neuroendocrine tumors
- Loss-of-function mutations in tumor suppressor genes such *PTEN* and *TSC2* (Chapter 7), which result in activation of the oncogenic mammalian TOR (mTOR) signaling pathway.
- Inactivating mutations in two genes, *alpha-thalassemia/mental retardation syndrome, X-linked* (*ATRX*) and death-domain associated protein (*DAXX*), which have multiple cellular functions, including telomere maintenance. Of note, nearly half of PanNETs have a somatic mutation in either *ATRX* or *DAXX*, but not both, suggesting that the encoded proteins function in a critical common pathway.

The three most common and distinctive clinical syndromes associated with functional pancreatic endocrine neoplasms are (1) *hyperinsulinism*, (2) *hypergastrinemia and the Zollinger-Ellison syndrome*, and (3) *multiple endocrine neoplasia (MEN)* (described in detail later).

Hyperinsulinism (Insulinoma)

β-cell tumors (insulinomas) are the most common of pancreatic endocrine neoplasms, and may produce sufficient insulin to induce clinically significant hypoglycemia. The characteristic clinical picture is dominated by hypoglycemic episodes, which occur if the blood glucose level falls below 50 mg/dL of serum. The clinical manifestations include confusion, stupor, and loss of consciousness. These episodes are precipitated by fasting or exercise and are promptly relieved by feeding or parenteral administration of glucose.

MORPHOLOGY

Insulinomas are most often found within the pancreas and are generally benign. Most are solitary, although multiple tumors may be encountered. *Bona fide* carcinomas, making up only about 10% of cases, are diagnosed on the basis of local invasion and distant metastases. On rare occasions an insulinoma may arise in ectopic pancreatic tissue. In such cases, electron microscopy reveals the distinctive granules of β-cells (Fig. 24-27).

Solitary tumors are usually small (often < 2 cm in diameter), encapsulated, pale to red-brown nodules located anywhere in the pancreas. Histologically, these benign tumors look remarkably like giant islets, with preservation of the regular cords of monotonous cells and their orientation to the vasculature. Not even the malignant lesions present much evidence of anaplasia, and they may be deceptively encapsulated. **Deposition of amyloid** is a characteristic feature of many insulinomas (Fig. 24-41).

Hyperinsulinism may also be caused by **focal or diffuse hyperplasia of the islets**. This change is found occasionally in adults but is far more commonly encountered as congenital hyperinsulinism with hypoglycemia in neonates and infants. Several clinical scenarios may result in islet hyperplasia (previously known as *nesidioblastosis*), including maternal diabetes, Beckwith-Wiedemann syndrome (Chapter 10), and rare mutations in the β-cell K^+-channel protein or sulfonylurea receptor. In maternal diabetes, the fetal islets respond to hyperglycemia by increasing their size and number. In the postnatal period, these hyperactive islets may be responsible for serious episodes of hypoglycemia. This phenomenon is usually transient.

Clinical Features. While up to 80% of islet cell tumors demonstrate excessive insulin secretion, the hypoglycemia is mild in all but about 20%, and many cases never become clinically symptomatic. The critical laboratory findings in insulinomas are high circulating levels of insulin and a high insulin-to-glucose ratio. Surgical removal of the tumor is usually followed by prompt reversal of the hypoglycemia.

It is important to note that there are many other causes of hypoglycemia besides insulinomas. The differential diagnosis of this metabolic abnormality includes such conditions as abnormal insulin sensitivity, diffuse liver disease, inherited glycogenoses, and ectopic production of insulin by certain retroperitoneal fibromas and fibrosarcomas. Depending on the clinical circumstances, hypoglycemia induced by self-injection of insulin should also be considered.

Zollinger-Ellison Syndrome (Gastrinomas)

Marked hypersecretion of gastrin usually has its origin in gastrin-producing tumors (*gastrinomas*), which are just as likely to arise in the duodenum and peripancreatic soft tissues as in the pancreas (so-called gastrinoma triangle). There has been lack of agreement regarding the cell of origin of these tumors, although it seems likely that endocrine cells of either the gut or the pancreas could be the source. Zollinger and Ellison first called attention to the **association of pancreatic islet cell lesions, hypersecretion of gastric acid and severe peptic ulceration**, which are present in 90% to 95% of patients.