Multiple Endocrine Neoplasia, Type 2

MEN-2 is subclassified into three distinct syndromes: MEN-2A, MEN-2B, and familial medullary thyroid cancer.

- *MEN-2A*, or *Sipple syndrome*, is characterized by *pheochromocytoma*, *medullary carcinoma of the thyroid*, and *parathyroid hyperplasia* (Table 24-11). Medullary carcinomas of the thyroid occur in almost 100% of patients. They are usually multifocal and are virtually always associated with foci of C-cell hyperplasia in the adjacent thyroid. The medullary carcinomas may elaborate calcitonin and other active products and are usually clinically aggressive. Among individuals with MEN-2A, 40% to 50% have pheochromocytomas, which are often bilateral and may arise in extra-adrenal sites. Parathyroid hyperplasia and evidence of hypercalcemia or renal stones occur in 10% to 20% of patients. **MEN-2A is clinically and genetically distinct from MEN-1 and is caused by germline gain-of-function mutations in the *RET* proto-oncogene on chromosome 10q11.2**. As was noted earlier, the *RET* proto-oncogene encodes a receptor tyrosine kinase that binds *glial-derived neurotrophic factor* (GDNF) and other ligands in the GDNF family and transmits growth and differentiation signals (Chapter 7). *Loss-of-function* mutations in *RET* result in intestinal aganglionosis and Hirschsprung disease (Chapter 17). In contrast, in MEN-2A (as well as in MEN-2B), germline mutations constitutively activate the RET receptor.
- *MEN-2B* has significant clinical overlap with MEN-2A. Patients develop medullary thyroid carcinomas, which are usually multifocal and more aggressive than in MEN-2A, and pheochromocytomas. However, unlike in MEN-2A, primary hyperparathyroidism is not present. In addition, MEN-2B is accompanied by *neuromas* or ganglioneuromas involving the skin, oral mucosa, eyes, respiratory tract, and gastrointestinal tract, and a *marfanoid habitus*, with long axial skeletal features and hyperextensible joints (Table 24-11). A germline mutation leading to a single amino acid change in RET, distinct from the mutations that are seen in MEN-2A, seems to be responsible for virtually all cases of MEN-2B. This point substitution affects a critical region of the tyrosine kinase domain of the protein and leads to constitutive activation of RET in the absence of ligand. Of note, approximately a third of sporadic medullary thyroid carcinomas harbor the identical mutation, and these cases are associated with aggressive disease and an adverse prognosis.
- *Familial medullary thyroid cancer* is a variant of MEN-2A, in which there is a strong predisposition to medullary thyroid cancer but not the other clinical manifestations of MEN-2A or MEN-2B. A substantial majority of cases of medullary thyroid cancer are sporadic, but as many as 20% may be familial. Familial medullary thyroid cancers develop at an older age than those occurring in the full-blown MEN-2 syndrome and follow a more indolent course.

In contrast to MEN-1, in which the long-term benefit of early diagnosis by genetic screening is not well established, diagnosis via screening of at-risk family members in MEN-2A kindred is important because medullary thyroid carcinoma is a life-threatening disease that can be prevented by early thyroidectomy. Now, routine genetic testing identifies *RET* mutation carriers earlier and more reliably in MEN-2 kindreds; all individuals carrying germline RET mutations are advised to undergo prophylactic thyroidectomy to prevent the inevitable development of medullary carcinomas.

PINEAL GLAND

The rarity of clinically significant lesions (virtually only tumors) justifies brevity in the consideration of the pineal gland. It is a minute, pinecone-shaped organ (hence its name), weighing 100 to 180 mg and lying between the superior colliculi at the base of the brain. It is composed of a loose, neuroglial stroma enclosing nests of epithelial-appearing *pineocytes*, cells with photosensory and neuroendocrine functions (hence the designation of the pineal gland as the "third eye"). Silver impregnation stains reveal that these cells have long, slender processes reminiscent of primitive neuronal precursors intermixed with the processes of astrocytic cells. The principal secretory product of the pineal gland is melatonin, which is involved in the control of circadian rhythms, including the sleep-wake cycle; hence the popular use of melatonin for the treatment of jet lag.

All tumors involving the pineal are rare; most (50% to 70%) arise from sequestered embryonic germ cells (Chapter 28). They most commonly take the form of so-called *germinomas*, resembling testicular seminoma (Chapter 21) or ovarian dysgerminoma (Chapter 22). Other lines of germ cell differentiation include embryonal carcinomas; choriocarcinomas; mixtures of germinoma, embryonal carcinoma, and choriocarcinoma; and, uncommonly, typical teratomas (usually benign). Whether to characterize these germ cell neoplasms as pinealomas is debated, but most "pinealophiles" favor restricting the term *pinealoma* to neoplasms arising from the pineocytes.

Pinealomas

These neoplasms are divided into two categories, pineoblastomas and pineocytomas, based on their level of differentiation, which, in turn, correlates with their aggressiveness. These tumors are rare, and are described in specialized texts.

SUGGESTED READINGS

Pituitary

Asa SL, Ezzat S: The pathogenesis of pituitary tumors. *Annu Rev Pathol* 4:97–126, 2009. [*A somewhat dated but excellent review on the molecular genetics of pituitary tumors by two foremost experts in this area*]