Peripheral nerve sheath tumors have several unique features. One is their association with relatively common familial tumor syndromes, including neurofibromatosis type 1 (NF1), neurofibromatosis type 2 (NF2), and schwannomatosis. Furthermore MPNSTs seen in the context of NF1 are thought to arise through malignant transformation of preexisting benign plexiform neurofibromas. Although malignant transformation of a preexisting benign lesion is a common origin for certain carcinomas (e.g., colon cancer), it is unusual in soft tissue tumors. Tumors with skeletal muscle differentiation are discussed in Chapter 26.

Schwannomas

These are benign tumors that exhibit Schwann cell differentiation and often arise directly from peripheral nerves. Schwannomas are a component of NF2, and even sporadic schwannomas are commonly associated with inactivating mutations in the *NF2* gene on chromosome 22. Loss of expression of the *NF2* gene product, *merlin*, is a consistent finding in all schwannomas. Merlin normally restricts the cell-surface expression of growth factor receptors, such as EGFR, through interactions involving the actin cytoskeleton; in its absence, cells hyperproliferate in response to growth factors.

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Schwannomas are well-circumscribed, encapsulated masses that abut the associated nerve without invading it, a feature that simplifies surgical excision. Grossly, these tumors form firm, gray masses. Microscopically, they are comprised of an admixture of dense and loose areas referred to as **Antoni A** and **Antoni B** areas, respectively (Fig. 27-14*A*). The dense eosinophilic Antoni A areas often contain spindle cells arranged into cellular intersecting fascicles. Palisading of nuclei is common and "nuclear-free zones" that lie between the regions of nuclear palisading are termed **Verocay bodies** (Fig. 27-14*B*). In the loose, hypocellular **Antoni B** areas the spindle cells are spread apart by a prominent myxoid extracellular matrix that may be associated with microcyst formation. Schwann cells are characterized by the presence of a spindled elongated nucleus with a wavy or buckled shape. Electron microscopy shows basement membrane deposits encasing single cells and collagen fibers. Because the lesion displaces the nerve of origin as it grows, silver stains or immunostains for neurofilament proteins demonstrate that axons are largely excluded from the tumor, although they may become entrapped in the capsule. The Schwann cell origin of these tumors is borne out by their uniform immunoreactivity for S-100. A variety of degenerative changes may be found in schwannomas, including nuclear pleomorphism, xanthomatous change, vascular hyalinization, cystic change, necrosis and mitotic activity. Some large mitotically active Schwannomas lacking Antoni B areas may mimic a sarcoma. Schwannomas may recur locally if incompletely resected, but malignant transformation is extremely rare (in contrast to plexiform neurofibromas, discussed later).

Clinical Features. Most Schwannomas cause symptoms by local compression of the involved nerve or adjacent structures (e.g., brainstem or spinal cord). Within the cranial vault, most schwannomas occur at the cerebellopontine angle, where they are attached to the vestibular branch of the eighth nerve. Affected individuals often present with tinnitus and hearing loss; the tumor is commonly referred to as an *acoustic neuroma*—a double misnomer, since the tumor neither arises from the acoustic portion of the nerve nor is it a neuroma. Elsewhere within the dura, sensory nerves are preferentially involved, including branches of the trigeminal nerve and dorsal roots. When extradural, schwannomas can arise in association with large nerve trunks or as soft tissue lesions without an identifiable associated nerve. Surgical removal is curative.

Neurofibromas

Neurofibromas are benign nerve sheath tumors that are more heterogeneous in composition than schwannomas. *The neoplastic Schwann cells are admixed with perineurial-like cells, fibroblasts, mast cells, and CD34+ spindle cells.* Neurofibromas may be either sporadic or NF1-associated. Different types of neurofibroma can be distinguished depending on their growth pattern.

- *Superficial cutaneous neurofibromas* often present as pedunculated nodules that can be seen isolated (if sporadic) or multiple (if NF1-associated).
- *Diffuse neurofibromas* often present as a large plaquelike elevation of skin and are typically NF1-associated.
- *Plexiform neurofibromas* can be found in deep or superficial locations in association with nerve roots or large nerves and are uniformly NF1-associated.

Pathogenesis. Only the Schwann cells in neurofibromas show complete loss of the *NF1* gene product, neurofibromin, indicating that these are the neoplastic cells. You will recall from Chapter 7 that neurofibromin is a tumor suppressor that inhibits RAS activity by stimulating the activity of a GTPase (RAS is active only when bound to GTP). Haploinsufficiency for the NF1 gene in other associated cells may also contribute to the growth of NF1-associated tumors. For example, there is evidence that NF1-haploinsufficient mast cells are hypersensitive to KIT ligand produced by Schwann cells and in response secrete factors that stimulate Schwann cell growth. This form of tumor/stromal cell cross-talk may be targetable with inhibitors of the KIT receptor tyrosine kinase. Other studies suggest that plexiform neurofibromas and dermal neurofibromas arise from different neural crest derived precursor cells. With rare exceptions, transformation to MPNST is only seen in plexiform neurofibromas. The overall incidence of MPNST in NF1 patients is about 5% to 10%, but patients with large numbers of plexiform neurofibromas and large deletions in the NF1 gene are at higher risk.

MORPHOLOGY

Localized cutaneous neurofibroma. These are small, well-delineated but unencapsulated nodular lesions that arise in the dermis and subcutaneous fat. They have relatively low cellularity and contain bland Schwann cells admixed with stromal cells such as mast cells, perineurial cells, CD34+ spindle cells, and fibroblasts. Adnexal structures are sometimes entrapped at the edges of the lesion. The stroma of these tumors contains loose collagen.