of spindle cells. At low power the tumor often appears "marbleized" due to variations in cellularity. Mitoses, necrosis, and nuclear anaplasia are common. An interesting phenomenon observed in MPNST is described as "divergent differentiation." This term refers to the presence of focal areas that exhibit other lines of differentiation, including glandular, cartilaginous, osseous, or rhabdomyoblastic morphology. A tumor exhibiting the latter is referred to as **Triton tumor**. Due to the poorly differentiated nature of MPNST, the distinction from an undifferentiated sarcoma may not be straightforward. Helpful clues include a diagnosis of NF1 in the affected patient and a clearly demonstrated anatomic relationship to a nerve or to a preexisting neurofibroma.

Neurofibromatosis Type 1 and Type 2

Neurofibromatosis Type 1

This is a common autosomal dominant disorder with a frequency of 1 in 3000. It is a systemic disease associated with nonneoplastic manifestations and with a variety of tumors, including neurofibromas of all types, malignant peripheral nerve sheath tumors, gliomas of the optic nerve, other glial tumors and hamartomatous lesions, and pheochromocytomas. Other features include mental retardation or seizures, skeletal defects pigmented nodules of the iris (*Lisch nodules*), and cutaneous hyperpigmented macules *(café au lait spots)*. The disease is caused by loss-of-function mutations in the *NF1* gene, located at 17q11.2, which encodes the tumor suppressor neurofibromin. The neoplastic cells in NF1-related tumors lack neurofibromin due to biallelic defects in the *NF1* gene. As has been mentioned earlier, NF-1 protein has GTPase activity that restrains RAS function. In the absence of NF-1, RAS remains trapped in its active state.

The disease has a high penetrance but variable expressivity. Some patients exhibit only subtle features, while others show disease that is restricted to certain parts of the body, a distribution that is attributable to mosaicism. An unfortunate subset has severe disease. Large chromosomal deletions that span *NF1* and extend to involve adjacent genes tend to be associated with more severe phenotypes.

Neurofibromatosis Type 2

This is an autosomal dominant disorder resulting in a range of tumors, most commonly bilateral eighth-nerve schwannomas and multiple meningiomas. Gliomas, typically ependymomas of the spinal cord, also occur in these patients. Many individuals with NF2 also have nonneoplastic lesions, which include nodular ingrowth of Schwann cells into the spinal cord (schwannosis), meningioangiomatosis (a proliferation of meningeal cells and blood vessels that grows into the brain), and glial hamartia (microscopic nodular collections of glial cells at abnormal locations, often in the superficial and deep layers of cerebral cortex). This disorder is much less common than NF1, having a frequency of 1 in 40,000 to 50,000. Certain other rare familial syndromes are also associated with multiple schwannomas, such as schwannomatosis and Carney complex.

The *NF2* gene is located on chromosome 22q12, and is also commonly mutated in sporadic meningiomas and schwannomas. The *NF2* gene product, merlin, is a cytoskeletal protein that appears to regulate membrane receptor signaling. Its tumor suppressive function may be related to a role in contact inhibition of cell growth. There is some correlation between the type of mutation and clinical symptoms, with nonsense and frameshift mutations causing more severe phenotypes than missense mutations.

KEY CONCEPTS

Peripheral Nerve Sheath Tumors

- The three common peripheral nerve sheath tumors—Schwannoma, neurofibroma, and malignant peripheral nerve sheath tumor—all likely arise from cells of Schwann cell lineage.
- Schwannomas are encapsulated benign tumors that can be associated with NF2.
- Neurofibromas are benign peripheral nerve sheath tumors sometimes associated with NF1 that can be subtyped as localized cutaneous, diffuse, or plexiform.
- Malignant peripheral nerve sheath tumors can be de novo sporadic neoplasms or NF1-associated tumors arising through malignant transformation of a (plexiform) neurofibroma.

SUGGESTED READINGS

Neuropathies and Other Non-Neoplastic Disorders of Peripheral Nerves

Dalakas MC: Advances in the diagnosis, pathogenesis and treatment of chronic inflammatory demyelinating polyneuropathy. *Nat Rev Neurol* 7:507, 2011. *[Review of CIDP with discussion of immune-pathogenesis.]*

Espinos C, Calpena E, Martinez-Rubio D, et al: Autosomal recessive Charcot-Marie-Tooth neuropathy. *Adv Exp Med Biol* 724:61, 2012. *[review of Charco-Marie-Tooth disease discussing the classification and genetic diversity.]*

Grantz M, Huan MC: Unusual peripheral neuropathies. Part I: extrinsic causes. *Semin Neurol* 30:387, 2010. *[Review of acquired extrnisic neuropathies including toxic, infectious and metabolic forms from a pragmatic clinical persepctive.]*

Koike H, Tanaka F, Sobue G: Paraneoplastic neuropathy: wide-ranging clinicopathological manifestations. *Curr Opin Neurol* 24:504, 2011. *[Review of paraneoplastic neuropathies with focus on clinical presentation and management.]*

Manji H: Toxic neuropathy. *Curr Opin Neurol* 24:484, 2011. *[Review of mechanisms of toxic neuropathies and their clinical manifestations with focus on chemotherapy induced forms.]*

Robinson-Papp J, Simpson DM: Neuromuscular diseases associated with HIV-1 infection. *Muscle Nerve* 40:1043, 2009. *[Discussion of peripheral neuropathy and myopathy as they develop at different stages of HIV.]*

Vallat JM, Funalot B, Magy L: Nerve biopsy: requirements for diagnosis and clinical value. *Acta Neuropathol* 121:313, 2011. *[Review of the pathologist's approach to peripheral nerve biopsies.]*

Muscular Dystrophies and Other Disorders of Muscle

Broglio L, Tentorio M, Cotelli MS, et al: Limb-girdle muscular dystrophy-associated protein diseases. *Neurologist* 16:340, 2010. *[Review of the classification of limb girdle mucular dystrophies.]*

Dimachkie MM: Idiopathic inflammatory myopathies. *J Neuroimmunol* 231:32, 2011. *[Review of inflammatory myopathies including clinical features and pathobiology.]*