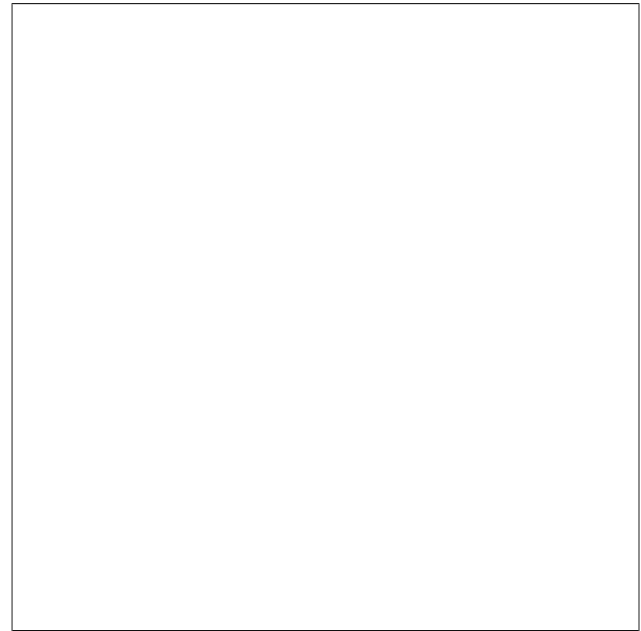


24-3. Plexiform NF involving cervical nerve roots is depicted on graphic (left), coronal STIR scan (right).



24-4. Coronal autopsy (left) and coronal STIR (right) show plexiform NF of thoracolumbar nerve roots (autopsy courtesy R Hewlett, MD).

"Localized" NF1 is caused by a focal sporadic somatic mutation that is not transmitted genetically.

Pathology

A variety of nonneoplastic as well as benign and malignant tumors are associated with NF1. Each is discussed below.

Nonneoplastic CNS Lesions. Multiple waxing and waning dysplastic white matter lesions on T2/FLAIR MRI are commonly identified in patients with NF1 (see below). Histopathologically these lesions represent myelin vacuolization and dysgenesis, not hamartomas.

Uncommon nonneoplastic CNS lesions include macrocephaly and subependymal glial nodules. Hydrocephalus occurs in 10-15% of cases. Dural ectasia may cause dilatation of the optic nerve sheaths, Meckel cave, or internal auditory canals.

Arteriopathy occurs in at least 6% of cases. The most common manifestation is progressive intimal fibrosis of the supraclinoid internal carotid arteries resulting in moya-moya. Both intra- and extracranial aneurysms and arteriovenous fistulae occur in NF1 but are relatively rare. The vertebral arteries are more commonly affected than the carotid arteries.

Nervous System Neoplasms. A spectrum of both benign and malignant peripheral nerve tumors occurs in NF1. All involve tumorigenesis of neural crest-derived cells

Neurofibromas. A spectrum of NF1-associated neurofibromas (NFs) occurs. Tumors derived from skin sen-

sory nerves are designated as dermal or **cutaneous neurofibromas**. Cutaneous neurofibromas increase with age so over 95% of adults with NF1 have one or more lesions. Cutaneous NFs are benign tumors that are mostly composed of Schwann cells and fibroblasts. Most are localized, well-circumscribed, discrete but unencapsulated tumors restricted to a single nerve ending.

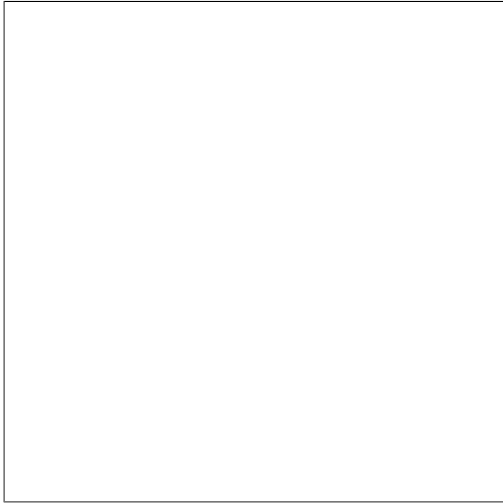
Less commonly, tumors within larger nerves appear as a more diffuse mass within the dermis (**"diffuse" cutaneous neurofibroma**).

Plexiform neurofibromas (PNFs) are virtually pathognomonic of NF1. PNFs are generally large, bulky tumors that are usually associated with major nerve trunks and plexi. PNFs are found in 30-50% of patients with NF1. PNFs appear as "rope-like" diffusely-infiltrating noncircumscribed lesions that resemble a "bag of worms."

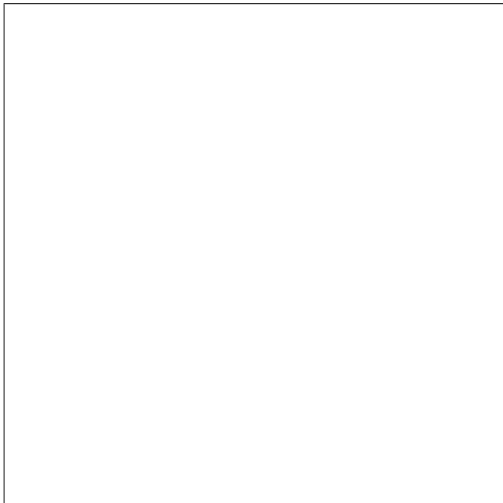
Spinal neurofibromas are found in approximately 40% of patients with NF1.

Histologically, NFs are comprised of small ovoid to spindle cells with dark wavy nuclei in a variably myxoid or collagenous background and are S100 positive. Nuclear atypia or rare mitotic figures in isolation should not be construed as signs of malignancy.

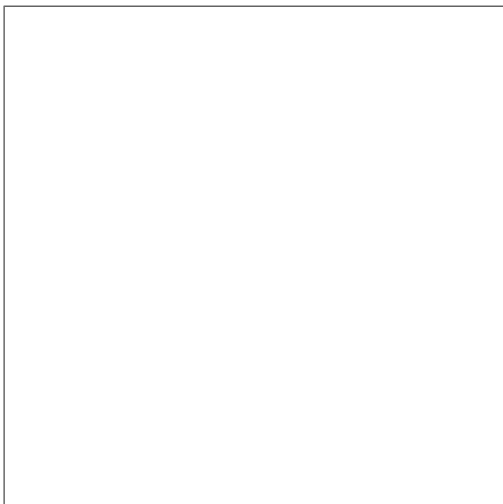
Malignant Peripheral Nerve Sheath Tumors. While most PNFs remain benign, between 10-15% become malignant. Deep-seated PNFs are at particular risk for development **MPNST**. MicroRNA misregulation appears to be a critical event in the malignant transformation of PNFs.



24-5. Axial T1WI shows multiple small cutaneous NFs in an adult with NF1.



24-6. T1C+FS scan in the same case shows the cutaneous NFs enhance strongly.



24-7. Optic nerve glioma in NF1 (top), axial T2WI (bottom) show fusiform enlargement of the optic nerve. Nerve sheaths are moderately enlarged.

MPNSTs that occur in the setting of NF1 tend to occur at a younger age and may also include rhabdomyoblastic and other heterologous elements. These tumors--referred to as **malignant Triton tumors**--are very characteristic of NF1.

Gliomas. The vast majority of gliomas in NF1 are **pilocytic astrocytomas**. While they can arise anywhere in the CNS, the optic nerve is the most common site (optic pathway "glioma" or OPG). OPG occurs in 15-20% of patients with NF1 and can be uni- or bilateral. Some OPGs involve the optic chiasm and optic tracts. In contrast to most sporadic diffusely-infiltrating pontine "gliomas," NF1-associated gliomas of the medulla, tectum, and pons are typically more benign.

Approximately 20% of NF1-associated gliomas are malignant. These include **diffusely-infiltrating ("low grade") fibrillary astrocytoma**, **anaplastic astrocytoma**, and **glioblastoma multiforme**.

Non-CNS Neoplasms. NF1 is associated with an increased risk of leukemia (especially juvenile myelomonocytic leukemia and myelodysplastic syndromes), gastrointestinal stromal tumors (6%), and adrenal or extra-adrenal pheochromocytoma (0.1-5%).

NF1-ASSOCIATED NEOPLASMS

Common

- Cutaneous neurofibromas (95% of adults)
- Plexiform neurofibroma (30%)
- Spinal neurofibromas

Less Common

- Optic pathway glioma (15-20%)
 - # 80% pilocytic astrocytoma
- Other astrocytomas (20%)
 - # Diffusely-infiltrating fibrillary astrocytoma (WHO grade II)
 - # Anaplastic astrocytoma (WHO grade III)
 - # Glioblastoma multiforme

Rare But Important

- Malignant peripheral nerve sheath tumor (develop in 10-15% of PNFs)
- Rhabdomyosarcoma
- Juvenile chronic myeloid leukemia
- Juvenile xanthogranuloma
- Gastrointestinal stromal tumor
- Melanoma
- Thyroid medullary carcinoma
- Pheochromocytoma

Clinical Issues

Epidemiology and Demographics. NF1 is the most common of all the inherited tumor syndromes and is one of the most common CNS single gene disorders, affecting 1/2500-300 live births. There is no gender predilection.