Schwannoma

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Definition

Schwannoma is a tumor originating from Schwann cells and is classified among benign soft tissue tumors, although one of its variants (i.e., melanotic Schwannoma → see dedicated section) is potentially malignant.

The benign version is also known as conventional Schwannoma, neurilemmoma, neurinoma, and neuroma.

Epidemiology and Presentation

Schwannoma is a relatively common tumor affecting all ages (peak incidence in the fourth to sixth decades of life) without gender prevalence. Along with neurofibroma (→ see dedicated section), it is the most common type of benign peripheral nerve tumor in adults. It most frequently arises along the peripheral nerves of the skin and subcutis, with special regard to the extremities (mainly flexor surfaces) and head and neck. Paraspinal extramedullary lesions (e.g., mediastinal or retroperitoneal lesions of the paravertebral space) can grow through neural foramina (known as dumbbell tumor or hourglass tumor), compress adjacent structures (e.g., vessels, nerve roots, ureters), and cause bone erosion.

Although less frequently, the tumor can locate intracranially: 85% of these schwannomas develop in the cerebellopontine angle as they originate from the vestibular component of the eighth cranial nerve (acoustic nerve neurinoma or acoustic neuroma or vestibular neuroma; for more details → see section entitled "Acoustic Neuroma"). Schwannomas of other sites (e.g., spinal intramedullary, central nervous system, bone, gastrointestinal lesions) are rare.

The tumor presents as a solitary slow-growing encapsulated well-circumscribed lesion (<10 cm in size), often asymptomatic (incidentaloma on imaging studies) as pain is more frequent in schwannomatosis (→ see next paragraph). At surgery, the lesion is attached to a (usually small) nerve in about 50% of cases. Paraspinal and

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intraspinal lesions can cause symptoms due to the compression of nerve roots or spinal cord; hearing loss and vertigo frequently precede the diagnosis of a vestibular schwannoma. Magnetic resonance imaging is considered the best imaging technique for this type of tumor.

Etiology and Predisposition

More than 90% of schwannomas are solitary and sporadic. Multiple schwannomas are a feature of three well-defined clinical conditions:

(a) **Neurofibromatosis type 2** is caused by inactivating mutations of the NF2 tumor suppressor gene, which encodes a protein called merlin (also known as schwannomin), which is expressed particularly in Schwann cells. This condition has an estimated incidence of 1 in 33,000 people and is considered to have an autosomal dominant pattern of inheritance. Patients with neurofibromatosis type 2 carry a germline mutation of a copy of NF2: in about 50% of cases, the altered gene is inherited from an affected parent, while the remaining cases result from new mutations in the NF2 gene (i.e., occur in patients without a family history of the disease). The biallelic inactivation of the NF2 gene is then acquired through a somatic mutation. Of note, up to 33% of individuals with a de novo pathogenic NF2 variant have somatic mosaicism for the variant (somatic mosaicism refers to the occurrence of two genetically distinct populations of cells within an individual, derived from a postzygotic mutation; in contrast to inherited mutations, somatic mosaic mutations may affect only a portion of the body and are not transmitted to progeny): these individuals may have normal molecular genetic testing of NF2 in unaffected tissue (e.g., peripheral blood lymphocytes), and thus molecular genetic testing of tumor tissue may be necessary to establish the presence of somatic mosaicism. Patients with neurofibromatosis type 2 usually develop multiple schwannomas before the age of 30 years: in particular, bilateral vestibular schwannoma is the hallmark of neurofibromatosis type 2 (which is also known as bilateral acoustic neuroma, BAN). Patients may also develop meningioma (50% of patients; often multiple) and glioma (most frequently ependymoma of the cervical spinal cord). For criteria to diagnose neurofibromatosis type 2, → see Table 225.1.

(b) **Schwannomatosis** is the rarest form of neurofibromatosis (which includes neurofibromatosis type 1 and neurofibromatosis type 2). The features of schwannomatosis resemble those of neurofibromatosis type 2: however, schwannomatosis almost never includes vestibular schwannomas (a hallmark of neurofibromatosis type 2); moreover, unlike the other forms of neurofibromatosis, schwannomatosis is not associated with the development of other tumor types. Schwannomatosis usually becomes clinically apparent in early adulthood, the most common symptom being pain, which ranges from mild to severe. Other signs and symptoms depend on the location of the tumors and which nerves are affected (e.g., numbness, weakness, tingling). The life

Table 225.1 Criteria for diagnosis of neurofibromatosis type 2 (NF2)

1	Bilateral vestibular schwannoma <70 years	**Or**
2	First-degree relative family history of NF2 **and** unilateral vestibular schwannoma <70 years	**Or**
3	First-degree relative family history of NF2 **or** unilateral vestibular schwannoma **and** 2 of meningioma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification (if unilateral vestibular schwannoma plus =/> 2 non-intradermal schwannomas, negative LZTR1 test is needed[a])	**Or**
4	Multiple meningiomas (2 or more) **and** 2 of unilateral vestibular schwannoma, cataract, glioma, neurofibroma, schwannoma, cerebral calcification	**Or**
5	Constitutional or mosaic pathogenic NF2 gene mutation in blood **or** identical mutations in 2 distinct tumors	

[a]Ideally the LZTR1 test should be performed in the tumor, but blood test is still useful to rule out a germline schwannomatosis condition

expectancy of people with schwannomatosis is normal. Mutations in SMARCB1 and LZTR1 tumor suppressor genes are believed to cause schwannomatosis, although other genetic changes are likely needed to trigger the development of schwannomas. In this regard, the most common somatic aberrations in schwannomas are mutations in the NF2 gene and loss of chromosome 22 (where both SMARCB1, LZTR1, and NF2 are located). Most cases of schwannomatosis are sporadic, whereas only 15% of cases run in families. The familial cases have an autosomal dominant pattern of inheritance, which means a germline mutation in one copy of the SMARCB1 or LZTR1 gene greatly increases the risk of developing schwannomas (although the penetrance is not complete). Of note, germline inactivating mutations of SMARCB1 are also the cause of rhabdoid tumor predisposition syndrome (→ see section entitled "Rhabdoid Tumor").

(c) **Gorlin syndrome**: also known as Gorlin-Koutlas syndrome and nevoid basal cell carcinoma syndrome (NBCC), this cancer predisposition syndrome is characterized by the development of multiple cutaneous basal cell carcinomas (starting from adolescence or early adulthood) and keratocystic odontogenic tumors (which may cause painful facial swelling and tooth displacement). Other tumors associated with this syndrome are schwannomas, medulloblastoma, cardiac fibroma (10% of patients), and ovarian fibroma. The estimated prevalence of Gorlin syndrome is 1 in 30,000 people: of note, while more than 1 million new cases of basal cell carcinoma are diagnosed each year in the USA, fewer than 1% of these tumors are related with this syndrome. The causal gene is PTCH1 (located in chromosome 9), a tumor suppressor gene encoding patched-1 (a receptor for the ligand sonic hedgehog). The Gorlin syndrome is inherited in an autosomal dominant pattern: in most cases, the patient inherits a PTCH1 inactivating germline mutation from one affected parent (other cases result from new mutations in the PTCH1 gene and occur in people with no history of the disorder in their family). For the tumor to develop, a somatic mutation in the second copy of the PTCH1 gene must occur during the patient lifetime (according to the classical two-hit theory proposed for hereditary retinoblastoma).

Pathology

Conventional schwannoma is a nerve sheath tumor composed of well-differentiated Schwann cells. Most lesions are encapsulated biphasic tumors with compact areas of spindle cells (Antoni A tissue) with occasional palisading (parallel rows of Schwann cell nuclei; Verocay bodies are formed by a highly ordered arrangement of Schwann cell nuclei in rows separated by fibrillary processes), alternated with loosely arranged foci (Antoni B tissue). Cytoplasmic nuclear inclusions, nuclear pleomorphism, and mitotic figures may be observed. In a minority of cases, this biphasic pattern cannot be recognized, with some tumors showing predominantly Antoni B tissue, while others lacking it.

A neurinoma with degenerative nuclear atypia or extensive hyalinization is referred to as "ancient" schwannoma. Cellular schwannoma is composed almost exclusively of Antoni A tissue without Verocay bodies: these tumors most commonly locate in paravertebral space, mediastinum, retroperitoneum, and pelvis. Plexiform schwannoma, either biphasic or cellular, involves multiple nerve fascicles or a nerve plexus: this tumor usually is diagnosed earlier in life (e.g., childhood) and arises in the skin or subcutis. Microcystic/reticular schwannoma is the rarest variant of schwannoma and is characterized by a microcyst-rich network of interconnected bland spindle cells with scant eosinophilic cytoplasm and a myxoid, fibrillary, and/or hyalinized collagenous stroma. A variant called neurofibroma/schwannoma hybrid nerve sheath tumor has also been described, which is associated with larger nerves and occurs either sporadically or in the context of schwannomatosis or neurofibromatosis type 1 or 2 (→ see Chap. 128).

Due to occasional increased cellularity, hyperchromasia, presence of pleomorphic nuclei, and frequent mitotic figures, some cases of schwannoma can be misinterpreted as malignant tumors.

Differential diagnosis may be needed with the following: neurofibroma (→ see Table 225.2); leiomyoma and leiomyosarcoma (negative for S100, positive for

Table 225.2 Differential diagnosis between schwannoma and neurofibroma: clinicopathological features

	Schwannoma	Neurofibroma
Epidemiology	Age: 20–50 years Gender: M = F	Age: 20–40 years Gender: M = F
Etiology	Sporadic but may occur in NF2 > NF1	Sporadic, some in NF1
Pathology	Typically encapsulated; Antoni A and Antoni B areas (alternating hypercellular and hypocellular areas)	Usually no capsule; spindle cells, shredded carrot collagen, mast cells; hypocellular, myxoid areas without hypercellular areas
Plexiform variant	Less common	More common
Biomarkers	S100: strong and diffuse Calretinin: stronger CD34: scattered Factor XIIIa: negative/focal	S100: weaker Calretinin: focal CD34: stronger Factor XIIIa: stronger
Malignant potential	Malignant transformation: extremely rare	Malignant transformation occurs in 5–15% of patients with neurofibromatosis type 1

SMA and desmin); malignant peripheral nerve sheath tumor (infiltrative growth, hypercellular, pleomorphic nuclei, and high mitotic activity; areas of geographic necrosis can show divergent differentiation; staining for S100 is weak or negative); pleomorphic hyalinizing angiectatic tumor (no capsule, infiltrative border, large ectatic vascular spaces with perivascular hyalinization, fibrin within and around vessels; negative for S100 and CD31, positive for CD34); and solitary circumscribed neuroma (palisaded encapsulated neuroma; encapsulated dermal or subcutaneous tumor which may show nuclear palisading; silver stains show the axons traversing the Schwann cells: however, they are near the capsule in schwannomas; peripheral weak EMA positivity).

Biomarkers

Schwannoma typically stains diffusely positive for S100, whereas expression of GFAP (glial fibrillary acidic protein) is less common. Collagen IV and laminin are often diffusely positive. Staining for neurofilament protein is helpful to detect entrapped intratumoral axons (found in one third of sporadic schwannomas). Cytokeratins may be positive especially in retroperitoneal and mediastinal lesions. CD34 is often positive in subcapsular areas. Schwannoma stains negative for desmin and SMA (smooth muscle actin).

Complete or partial loss of chromosome 22 is the most common cytogenetic anomaly in schwannoma, and the loss of expression of merlin (also called neurofibromin 2 or schwannomin), the protein product of the NF2 tumor suppressor gene located at 22q12, is considered a key event in schwannoma tumorigenesis. Moreover, NF2 inactivating somatic mutations have been reported in about 60% of sporadic schwannomas.

Prognosis

Conventional schwannoma is a benign tumor which does not usually relapse after complete resection. Cellular and especially plexiform variants (which involve several nerve bundles) are less amenable to complete removal without nerve damage and sometimes can only be debulked: in these cases, disease recurrence is possible. Importantly, schwannoma is not considered a precursor of malignant peripheral nerve sheath tumor (MPNST), although exceptionally rare cases of malignant transformation have been reported.

Therapy

Surgical excision is the treatment of choice. Schwannoma usually does not infiltrate the associated nerve (typically originates from a single bundle within the main nerve and grows eccentrically displacing the rest of the nerve) so it can usually be

separated from it without nerve damage during surgical treatment; as the schwannoma grows larger, more fascicles are affected, making nerve damage more difficult to be avoided (of note, neurofibroma tends to form more centrally within the nerve). Stereotactic radiotherapy is being increasingly utilized for deep lesions difficult to reach/treat with surgery.

Asymptomatic deep schwannomas (e.g., retroperitoneal lesions) can be managed by image-based follow-up.

For patients with neurofibromatosis type 2 and progressive bilateral acoustic neurinomas, bevacizumab (a monoclonal antibody blocking VEGFA) is associated with hearing improvement and tumor shrinkage in 30–60% of cases.

Suggested Readings

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