Review

The pathobiologic spectrum of Schwannomas

Ö. Kurtkaya-Yapıcıer[1,2], B. Scheithauer[1] and J.M. Woodruff[3]

[1]Departments of Pathology and Laboratory Medicine, Mayo Clinic, Rochester, MN, [2]Marmara University School of Medicine, Istanbul, Turkey, and the [3]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Summary. In terms of their morphology, clinical associations and behavior, peripheral nerve sheath tumors are among the most varied of human neoplasm. Not surprisingly, such tumors are subject to frequent misdiagnosis. This is particularly true of the spectrum of schwannomas which include: a) conventional schwannoma, a histologically benign tumor which, on occasion, is destructive of surrounding osseous structures, b) the relatively recently described cellular schwannoma, a tumor that histologically simulates malignant peripheral nerve sheath tumor (MPNST), c) plexiform schwannoma which, particularly in cellular form and when occurring in childhood, simulates MPNST, and d) melanotic schwannoma which is often mistaken for melanoma. The psammomatous form of the latter is often associated with Carney complex, a rare heritable disorder that: a) includes cutaneous lentigines, b) myxomas of skin, subcutaneous tissue, and heart, c) and endocrine neoplasms. The tendency to misdiagnose schwannomas and to overestimate their grade makes schwannomas worthy of note. Herein, we discuss the four major schwannoma variants, their essential clinicopathologic features, and differential diagnosis. The distinction from MPNST is given particular attention.

Key words: Schwannoma, Morphology, Clinical associations, Differential diagnosis

Conventional schwannoma

General comments

Once termed "neurilemoma," (Stout, 1935), this most common variant of schwannoma, presents as a globoid, encapsulated tumor associated with a spinal or cranial sensory nerves. Its peak incidence spans the third through the sixth decades, no gender predilection being seen. Sites most affected include the head and neck,

flexor surfaces of extremities, and nerves. Visceral examples are rare (Prévot et al., 1999; Miettinen et al., 2001). Most schwannomas are solitary, but multiple schwannomas occur in two settings. Best known are bilateral 8th nerve schwannomas, in association with neurofibromatosis type (NF2). Less common are multiple schwannomas associated with a somatic mutation of the NF2 gene (MacCollin et al., 1996), a condition termed "schwannomatosis." Such patients lack a family history and do not have bilateral 8th nerve tumors. Instead, most are cutaneous or subcutaneous, but larger spinal as well as cranial nerves can be affected. Histologically, most tumors are of conventional type, but some are plexiform.

Macroscopic features

Clues to the diagnosis of schwannoma in its baseline form include globoid shape, presence of a capsule, tan color and homogeneously firm texture (Fig. 1A). Hemorrhage, cystic change, bright yellow areas rich in lipid-laden histiocytes, and fibrin accumulation may supervene (Fig. 1A), but frank necrosis is not a feature.

Microscopic features

Diagnostic features include a fibrous capsule, hyaline vessels, cellular (Antoni A) and loose textured (Antoni B) areas (Fig. 1B), Verocay bodies (opposing rows of spindle nuclei separated by anuclear rows of eosinophilic processes) (Fig. 1C). Retrogressive changes are common in large, old tumors, and include "degenerative nuclear atypia," vascular sclerosis and hemorrhage as well as occasional micronecroses (Fig. 1D,E). Microcyst formation, some with a pseudo-epithelial lining of plump Schwann cells (Fig. 1F), may also be seen.

Cyto/Molecular genetics

Mutations in the NF2 gene at position 22q12.2 are the basis of schwannoma formation both in sporadic schwannomas and in neurofibromatosis type 2 (Wolff et al., 1992). It is a tumor suppressor gene that codes for

Offprint requests to: B.W. Scheithauer, M.D., Division of Anatomic Pathology, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, USA. Fax (507) 284-1599

merlin (schwannomin), a cell membrane-associated protein that a) links the cell membrane and the cytoskeleton and b) functions in intracellular signaling pathways (Rouleau et al., 1993; Trofatter et al., 1993). Its decreased synthesis causes a disturbance of growth arrest through cell-cell contact. The nature of NF2 mutations varies; many are frameshift mutations and deletions that result in a truncated protein (Louis et al., 1995; Zucman-Rossi et al., 1998). Like the tumor suppressor gene NF1 that underlies neurofibroma formation, NF2 fulfills the "two-hit" hypothesis of tumorigenesis; loss of both wild-type alleles results in marked reduction of the gene product and tumor formation (Louis et al., 1995). Disease expression in neurofibromatosis type 2 correlates with the functional loss of merlin (Ruttledge et al., 1996).

Differential diagnosis

Mimics of conventional schwannoma include palisaded leiomyoma, palisaded myofibroblastoma of inguinal lymph nodes (PMILN) (Suster and Rosai., 1989; Weiss et al., 1989) and gastrointestinal stromal tumor (GIST). Palisaded leiomyoma usually presents in Müllerian tissues and is immunoreactive for desmin and smooth muscle actin. PMILN are S-100 protein immunonegative. Furthermore, no convincing examples of nodal schwannoma have been described. Lastly, GIST is usually immunoreactive for KIT (CD117) and is nonreactive for S-100 protein.
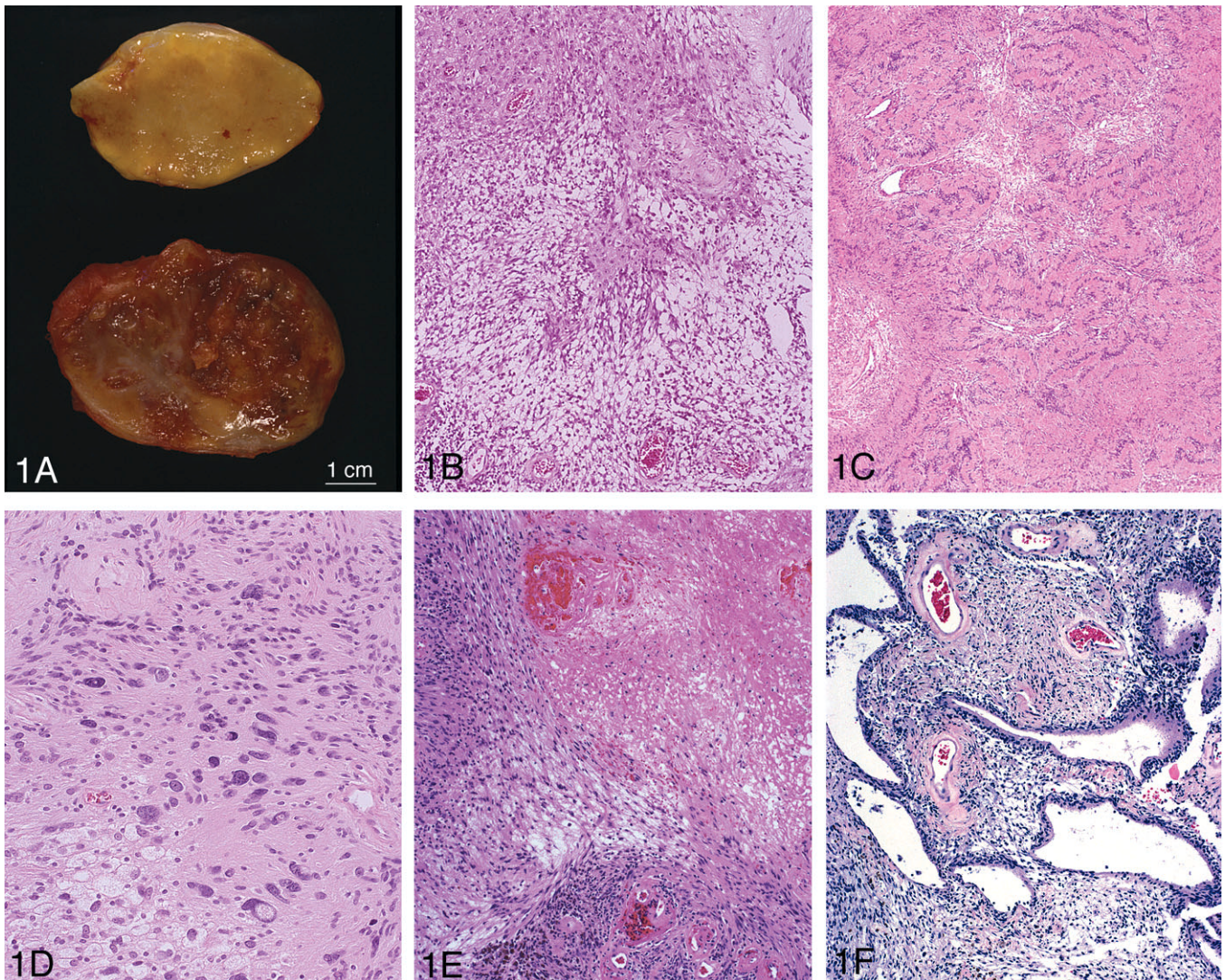
Fig. 1. Conventional schwannomas vary considerably in gross appearance, depending upon whether they lack (**A**, top) or possess degenerative changes (**A**, bottom). Microscopically, their baseline features include Antoni A and B patterns (**B**). Verocay bodies may be a conspicuous feature (**C**). Degenerative changes include nucleomegaly and hyperchromasia (**D**), vascular hyalinization, hemorrhage, hemosiderin deposits (**E**), as well as cystic degeneration sometimes with the formation of a pseudo-epithelial lining (**F**).

Prognosis and Clinical Behavior

Conventional schwannomas are benign but, when incompletely excised, occasionally recur. This is particularly true in "giant sacral schwannomas" and in the setting of NF2. There is no evidence that schwannomas grow during pregnancy (Beatty et al. 1995). Malignant transformation in conventional schwannoma is exceptionally rare (see below).

Malignancy in schwannoma

Of the variants of schwannoma under discussion, only the conventional form is known to undergo malignant transformation. This is a very rare occurrence (Woodruff et al., 1994) in which the tumor cells transform to either a) high-grade malignant epithelioid cells with abundant eosinophilic cytoplasm, vesicular nuclei and prominent nucleoli (Fig. 2A) or b) a malignant "small cell neuroepithelial" tumor (Fig. 2B). The former is more common and takes the form of either a) focal microscopic change occurring within the confines of the tumor and not going through the capsule, or b) tumors invasive of the capsule with involvement of surrounding soft tissues. Intratumoral microfoci of large cell transformation may be seen and has been termed "epithelioid malignant change" (EMC) (McMenamin and Fletcher, 2001); these appear to be of no prognostic significance. In contrast, when extensive and associated with transcapsular invasion, the tumor may be fatal (Woodruff et al., 1994), some giving rise to metastases. Cellular and plexiform schwannoma undergoing malignant change have not been described to date. Lastly, we suspect that when an MPNST arises in the setting NF2, it may well be a schwannoma having undergone malignant epithelioid cell transformation. Divergent differentiation includes the rare finding of cartilage and/or bone formation. Only a single example of rhabdomyosarcomatous and PNET differentiation has been described (Kurtkaya-Yapicier et al., 2003).

Angiosarcoma rarely develops within a conventional schwannoma (Trassard et al., 1996; Ruckert et al., 2000; McMenamin and Fletcher, 2001). Most are of the epithelioid type, thus, the distinction from schwannomas with epithelioid malignant cell change (see above) is necessary. The distinction is simple. Angiosarcomas stain not for S-100 protein, but for CD31, CD34 or both. The etiology of angiosarcoma in schwannomas likely relates to intratumoral vascular stasis (Trassard et al., 1996; Ruckert et al., 2000).
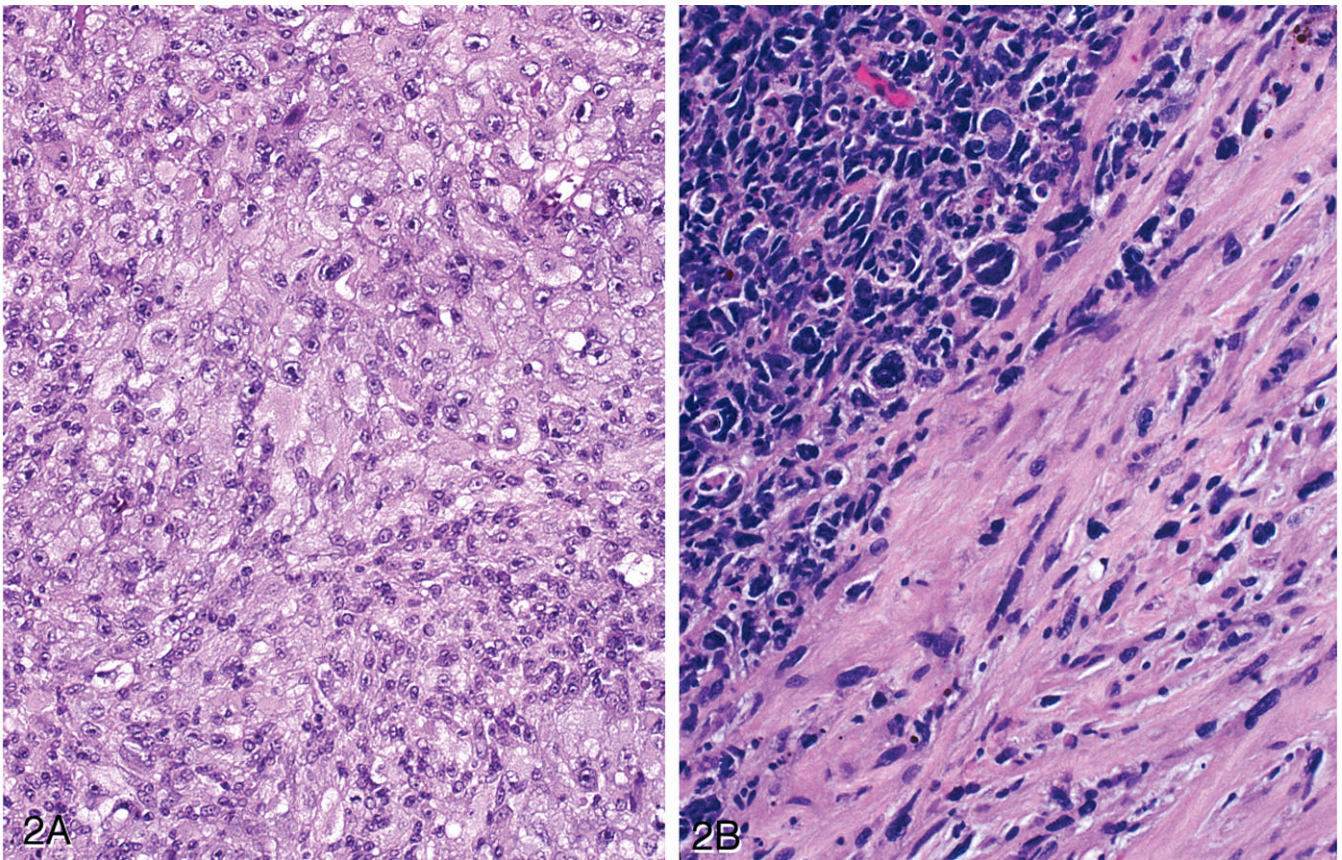
Fig. 2. Malignant transformation in schwannomas is rare and most often consists of transition to large, epithelioid cell cells **(A)**. Small cell transformation is less frequently seen **(B)**.
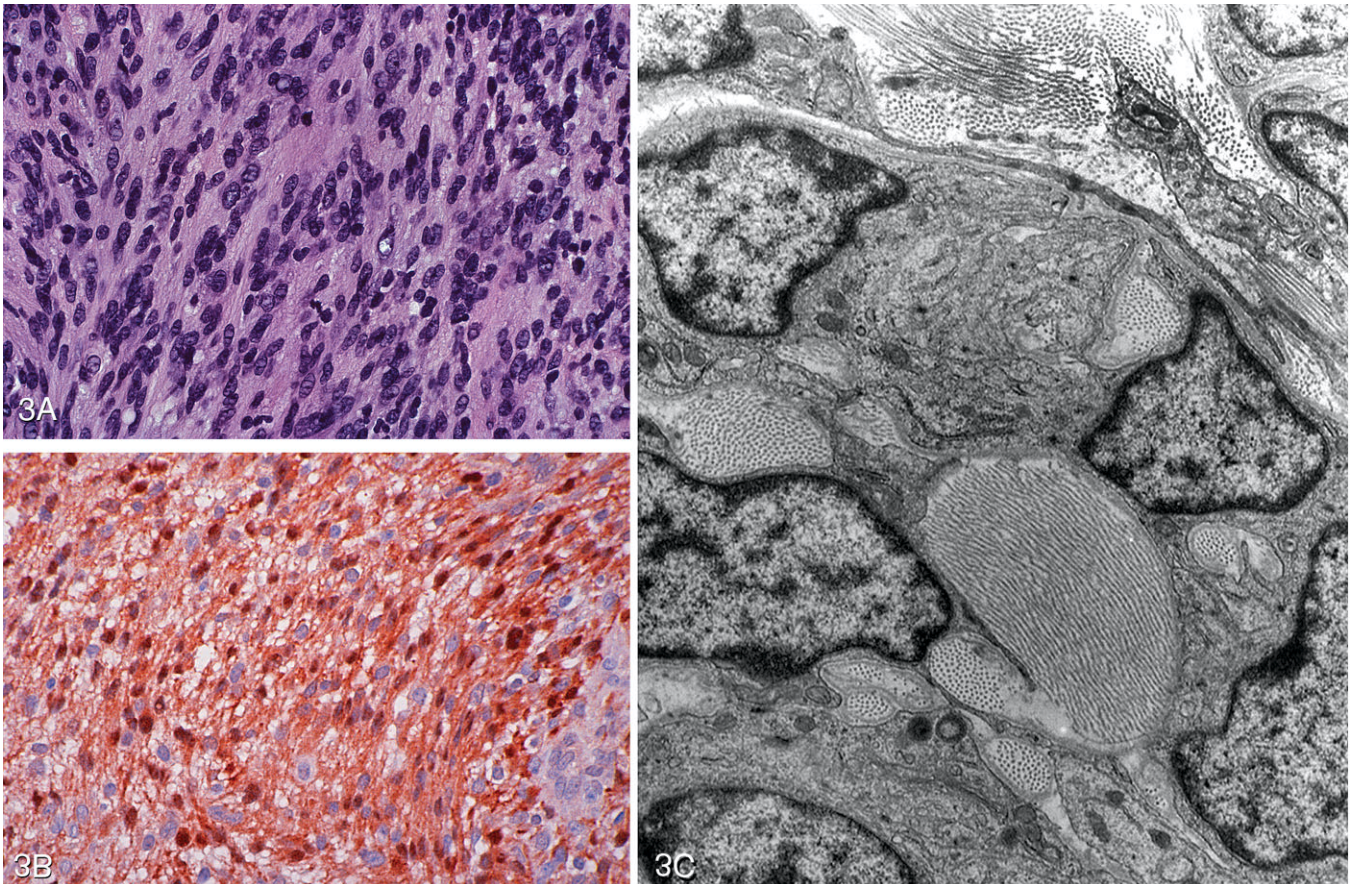
Cellular schwannoma

General comments

This now well-characterized form of schwannoma (Woodruff et al., 1981; Fletcher et al., 1987; White et al., 1990; Casadei et al., 1995) somewhat more often affects females and preferentially affects the posterior mediastinum and pelvis. Cranial and cutaneous nerves may also be involved. Less than 5% are NF-1 associated (White et al., 1990). Cellular schwannomas are benign and not evolving MPNSTs (see below).

Macroscopic features

Grossly, the tumors are globular and more solid than conventional schwannomas. Most have a relatively uniform, tan cut surface, with only occasional yellow patches. Hemorrhage is focal at most and necrosis is usually lacking. Occasional tumors are plexiform. Bone erosion may be seen, especially with sacral and paraspinal lesions.

Microscopic features

These cellular tumors consist mainly of spindle cells arrayed in fascicles, a storiform arrangement, or in a nonspecific pattern (Fig 3A). Like conventional schwannoma, they are also encapsulated. Lymphoid aggregates in the capsule or around vessels are a common finding, as are cellular whorls. The spindle cells are not as uniformly hyperchromatic as in high grade MPNST and have eosinophilic cytoplasm. Nuclear pleomorphism and significant hyperchromasia are only sometimes present. Rare examples exhibit microfoci of necrosis (White et al., 1990; Casadei et al., 1995). Other features shared with conventional schwannoma include hyalinized blood vessels, collections of lipid-laden histiocytes. and of course uniform S-100 protein immunoreactivity (Fig. 3C). The diagnosis is readily apparent on ultrastructure (Fig. 3C) which demonstrates pericellular basal lamina often demarcating collagen aggregates. Long spacing collagen is less frequently seen than in conventional schwannomas.

Fig. 3. Cellular schwannoma is a relatively common tumor characterized by Antoni A architecture, high cellularity, proliferative activity **(A)**. As in conventional schwannoma, uniform S-100 protein immunoreactivity is a reliable feature **(B)**. The same is true of Schwannian differentiation at the ultrastructural level. Note well-formed pericellular basal lamina **(C)**.

Differential diagnosis

The two tumors most often confused with cellular schwannoma are benign and low-grade malignant smooth muscle tumors and malignant peripheral nerve sheath tumors (MPNSTs). The distinction from smooth muscle tumors is easy since the latter are nonencapsulated, lack strong diffuse reactivity for S-100 protein, and are reactive for muscle markers. The differential with the conventional schwannoma and MPNST is summarized in Table 1.

Prognosis and clinical behavior

Although benign, cellular schwannomas may recur if incompletely excised. This is particularly true of proximally situated tumors involving spinal nerve roots within the spinal canal, sacral tumors, and intracranial lesions where the rate is 30-40% (Casadei et al., 1995). Only a rare example shows limited infiltration of surrounding tissues. To date, no cellular schwannoma has metastasized.

Plexiform schwannoma

General Comments

Whether conventional or cellular in histologic pattern, schwannomas may be multinodular or plexiform. Prior to its recognition as a schwannoma variant such tumors were often regarded as plexiform neurofibromas or MPNSTs arising therein (Harkin et al., 1978; Woodruff et al., 1983). Contributing to the confusion was a common feature, their lack of thick encapsulation, particularly in cutaneous examples (Fletcher and Davies, 1986). Unlike plexiform neurofibromas, there is no association with NF-1.

Macroscopic features

Plexiform schwannomas vary in size from small cutaneous tumors in which case their architecture may not be apparent, to sizable lesions (Fig. 4A), obviously consisting of firm, multinodular or "worm-like" components. Visceral examples are rare. As in conventional schwannomas, yellow discoloration may be seen in sizable tumors.

Microscopic features

Histologically, the contorted, plexiform profiles consist of typical Schwann cells, more Antoni A than B in pattern (Fig. 4B Hyalinized blood vessels occur in larger examples, but lymphoid aggregates and clusters of foamy histiocytes are usually absent. Mitoses are generally few or absent. As in all schwannomas, the tumor is uniformly S-100 protein positive. EMA reactivity is limited to perineurium surrounding the

Table 1. Conventional schwannoma, cellular schwannoma, and MPNST: differential diagnosis.

FINDINGS	CONVENTIONAL SCHWANNOMA	CELLULAR SCHWANNOMA	MPNST
Gross	Usually globoid encapsulated tumor that has abundant homogeneous light tan tissue, and may be cystic or hemorrhagic and show yellow patches. No gross necrosis.	Usually globoid encapsulated tumor, firmer than classic schwannoma and homogeneously tan. Occasional patches of yellow, but no gross necrosis.	Fusiform or globoid, pseudoencapsulated (infiltrative of surrounding tissues), firm, cream-tan, usually grossly necrotic tumor.
Microscopic	Antoni A and B areas with Verocay bodies; commonly find hyalinized and thick-walled blood vessels and lipid-laden histiocytes. Mitotic figures infrequent. Rarely see malignant transformation.	Mainly hypercellular Antoni A tissue. Cells are arranged in fascicles or whorls and may show marked hyperchromasia and nuclear pleomorphism. Notable are lymphoid deposits in capsule or perivascular area. Commonly find thick-walled blood vessels and collections of lipid-laden histiocytes. Rare foci of necrosis. Mitoses not uncommon but usually numbers no more than 4/10 HPF.	Markedly hypercellular, fasciculated, spindle cell tumor generally consisting of a uniform size and pronounced hyperchromasia. Geographic necrosis and mitotic counts in excess of 4/10 HPF are common. Epithelioid cells predominate in about 5 percent of tumors and 15 percent show heterologous glandular or sarcomatous elements.
Immunohisto-chemical	Diffuse and strong expression of S-100 protein.	Diffuse and strong expression of S-100 protein.	S-100 protein expression in scattered cells of 50-70 percent of cases.
Electron Microscopy	Well-differentiated cells with long, often interlacing cytoplasmic processes coated by basement membrane on their free surfaces. Intercellular long-spacing collagen common.	Similar to classic schwannoma. Increased cellularity. More nuclear atypia and occasional residual arrays of long, basement membrane-coated cytoplasmic processes. Long-spacing collagen less common.	Poorly differentiated cells with more pleomorphic nuclei, thick cytoplasmic processes, and sometimes patchy basement membrane. Long-spacing collagen rarely seen.
Clinical Behavior	May cause bone erosion and can recur if incompletely excised. Thus far 5 reported examples with malignant transformation that followed a malignant clinical course.	May cause bone erosion and recur if incompletely excised. Thus far no clinically malignant examples.	Has a proclivity to invade and destroy nearby soft tissues, recur locally, and metastasize distantly (usually to lung). About 90 percent are high-grade lesions.

profiles, but this may be scant. Axons are few or absent. Occasional mitoses may be seen, particularly in cellular tumors

Differential diagnosis

Since pediatric examples of this tumor can be sizable, cellular and proliferative (Fig 4C), they have been classified by some as MPNSTs (Meis-Kindblom and Enzinger, 1994). We disagree with this approach (Woodruff et al., 1995, 2003). Although such plexiform schwannomas with cellular features may locally recur, none have metastasized. The presence of four or more mitoses in many cases has been cited as evidence of malignancy but, as in cellular schwannoma, we do not find mitotic activity to be prognostically important in this lesion. Instead, local recurrence can be attributed to incomplete resection, focal lack of thick encapsulation, and irregular, finger-like tumor growth. Plexiform schwannomas occurring at any age group are benign and must not be called MPNST.

The differential diagnosis also includes plexiform neurofibroma, palisaded encapsulated neuroma (PEN), and neurotropic melanoma. Plexiform neurofibromas (Scheithauer et al., 1999) are often far less cellular, have a relatively mucin-rich matrix, and are less S-100 protein immunoreactive. Unlike plexiform schwannoma, PEN contains axons which are demonstrable on both silver impregnation (Bielschowsky and Bodian stain) and neurofilament immunostain. Plexiform schwannoma and neurotropic melanoma both affect skin and subcutaneous tissue. Given the marked difference in their prognoses, it is of great importance to distinguish the two. Neurotropic melanoma affects mainly the head and neck and often underlies an in situ cutaneous melanoma. Plexiform schwannomas tend to push parent nerve tissue aside, whereas in neurotropic melanoma the residual peripheral nerve is often easier to identify. Neurotropic melanoma involves epineurial tissue as tumor bundles, and also concentrates in the perineurium to form distinctive, concentric rings about the nerve. Neurotropic melanomas also have larger nuclei, ones more irregular in shape and markedly hyperchromatic when compared to those of plexiform schwannoma. Lastly, neurotropic melanoma is a desmoplastic lesion.

Prognosis and clinical behavior

Although plexiform schwannomas are entirely benign, a small proportion of incompletely excised tumors recur.

Melanotic schwannoma

General comments

This rare tumor shows a tendency to involve spinal nerves and paraspinal ganglia (Font et al., 1984; Scheithauer et al., 1999; Carney, 1990). Viscera may also be affected, particularly in cases associated with Carney's complex (Carney et al., 1985; Carney 1990). Their peak incidence is the 4th decade. About 10% of
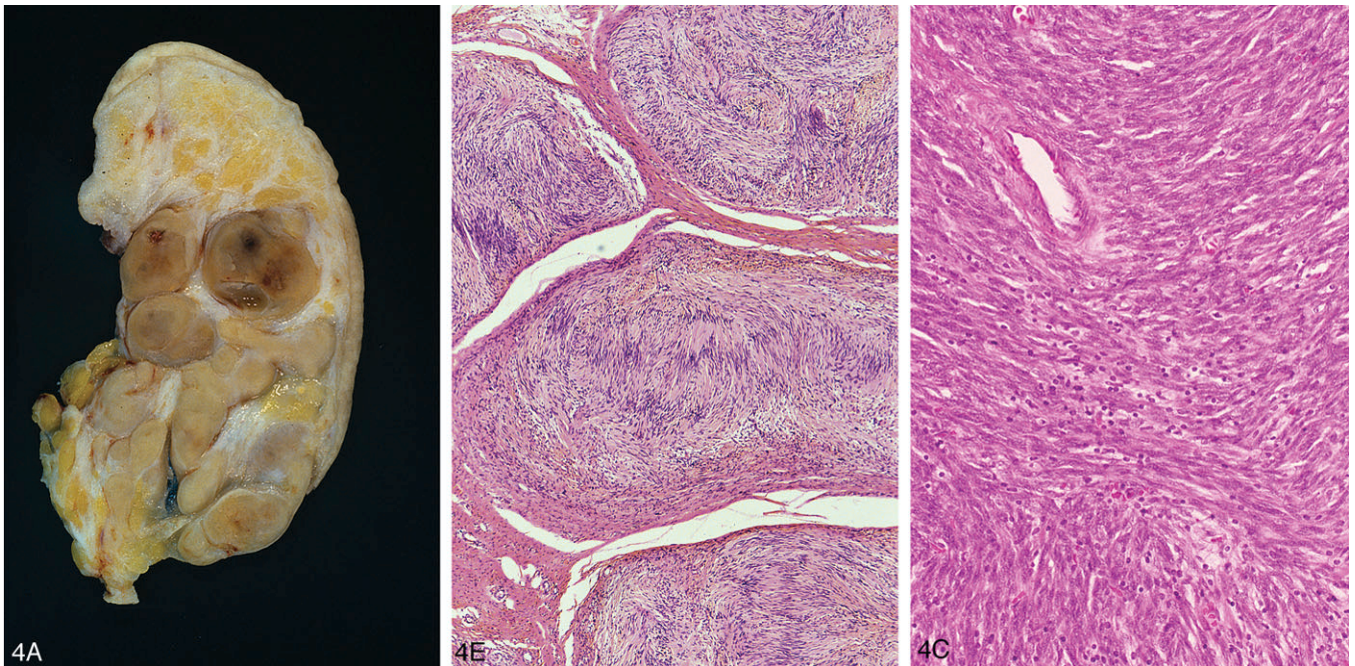
Fig. 4. Plexiform schwannoma may be multinodular or frankly worm-like **(A)** in architecture. The profiles of the enlarged nerves may be quite discrete and consist of obvious Schwann cells **(B)**. When cellular, such as this orbital example in a child **(C)**, they should not be mistaken for MPNST.

melanotic schwannomas are malignant.

Macroscopic features

Melanotic schwannoma is most often solitary and ovoid, but multifocal tumors may be seen, in which case they are usually malignant (Scheithauer et al., 1999). Covered at most by a thin fibrous membrane, their cut surface has the consistency of tar and varies from gray to pitch black (Fig. 5A). Erosion of adjacent bone may be seen.

Microscopic features

Histologically, melanotic schwannoma is characterized by plump spindle and epithelioid cells arranged in sheets, lobules, and interlacing fascicles (Fig. 5B) (Scheithauer et al., 1999). Although they have indistinct cell borders, a syncytial appearance may be seen. Cytoplasmic pigmentation varies greatly. Most pigmented are the often accompanying histiocytes ("melanophages"). Tumor cell nuclei are usually round to ovoid with delicate chromatin and a small nucleolus. Many melanotic schwannomas arise from paraspinal ganglia as evidenced of the presence of ganglion cells within or adjacent to the tumor. An ominous feature is the finding of macronucleoli (Fig. 5C). Necrosis, when seen, is often geographic in pattern and also suggests malignancy. Melanotic schwannomas associated with Carney complex (see below) feature psammoma bodies and adipose-like cells (Fig. 5D).

Cyto- /Molecular genetics

Studies of melanotic schwannomas associated with Carney complex, both heritable and sporadic, have found two gene loci to be involved in tumorigenesis. One locus is on chromosome 17 and the other on chromosome 2 (Stratakis et al., 2001). The 17q22-24 locus represents the tumor suppressor gene PRKAR1A that encodes the type 1 [alpha] regulatory subunit of protein kinase A (PKA) (Casey et al., 2000; Kirschner et al., 2000). Mutations in this gene are variable, but most result a truncated, nonfunctional protein (Kirschner et
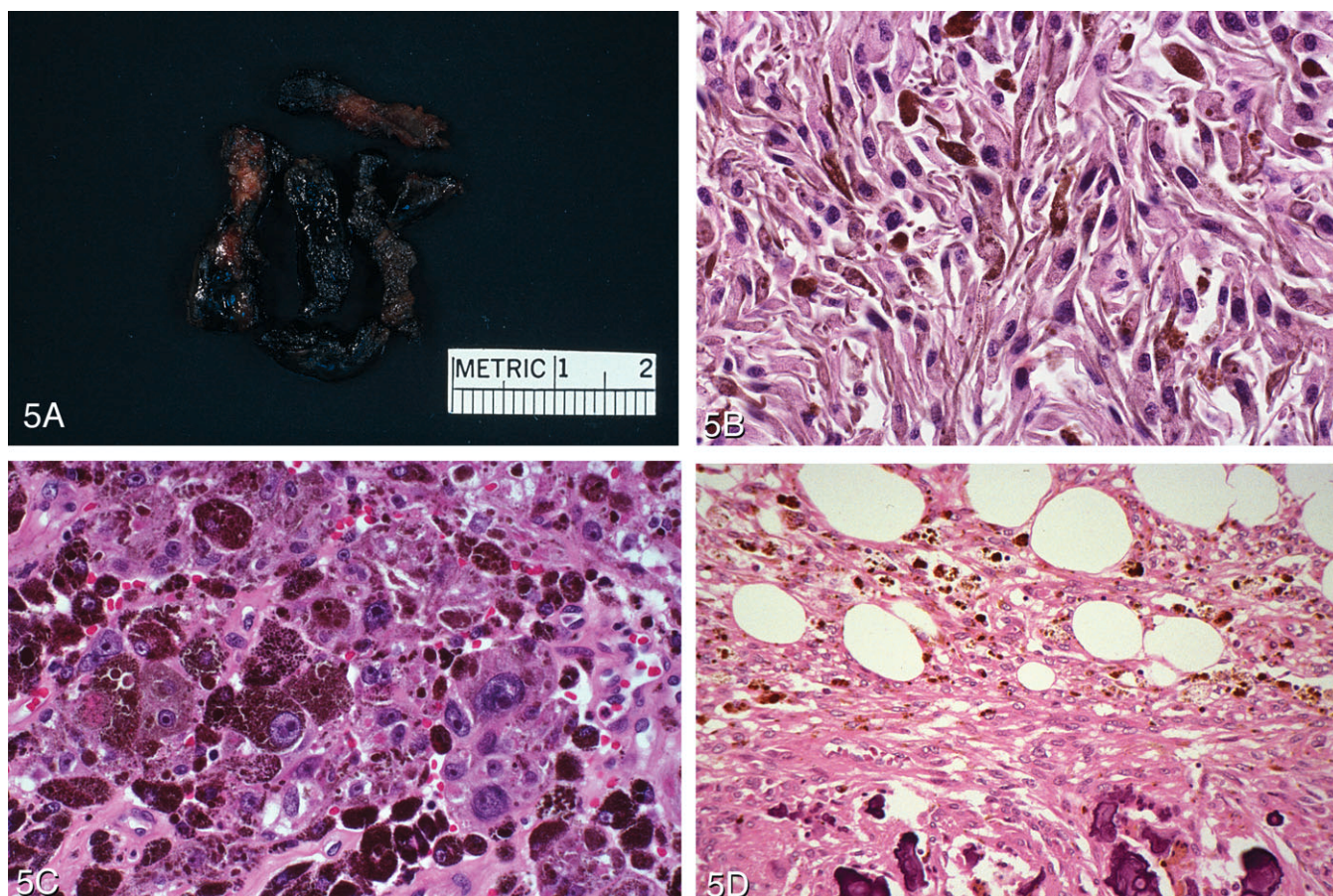
Fig. 5. Melanotic schwannomas are tar-like and lack a grossly defined capsule **(A)**. They consist of spindle to epithelioid cells often accompanied by densely pigmented melanophages **(B)**. Macronucleoli **(C)** and/or necrosis suggest malignancy, as does brisk mitotic activity. Psammoma bodies and cells resembling adipocytes typify the tumors of Carney complex **(D)**.

al., 2000). Alterations in the ratio of alpha and beta subunits result in an increased PKA response to cAMP stimulation, a factor believed to be important in tumorigenesis (Kirschner et al., 2000). Of cases without detectable abnormalities of chromosome 17, most show abnormalities at the 2p16 locus (Stratakis et al., 2001). These changes are not as well characterized, but genes at this locus are thought to have regulatory effects upon cell division (Stratakis et al., 1996a,b).

Differential diagnosis

The differential diagnosis of melanotic schwannoma includes conventional schwannoma and other pigmented lesions. These include pigmented neurofibroma, meningeal melanocytoma, metastatic melanoma, and clear cell sarcoma of soft parts. As a rule, melanotic schwannomas are easily distinguished from conventional schwannoma, since the former lack a distinct capsule, well-formed Verocay bodies, and clear-cut Antoni A and B areas. On the other hand, conventional schwannomas rarely involve the gastrointestinal tract and lack melanin, psammoma bodies, and fat. The gray-brown granular pigment sometimes seen in ordinary schwannomas is not melanin, but lipofuscin.

The differential with *pigmented neurofibroma* and other pigmented PNSTs (Payan et al., 1986) is more difficult. Pigmented neurofibromas are often of the diffuse type, vary in size, usually show only microscopic pigmentation, and lack both psammoma bodies and fat (Fetsch et al., 2000). Their nuclei are small and often elongate, unlike those of melanotic schwannoma, which tend to be round or ovoid with delicate chromatin and a distinct central nucleolus. The cytoplasm of melanotic schwannoma cells is rather abundant, whereas that of neurofibromas is scant. Immunostaining for S-100 protein is non-uniform in neurofibroma. Ultrastructurally, the cellular heterogeneity of neurofibroma contrasts with the uniform morphology of melanotic schwannoma.

Distinguishing melanotic schwannoma from *melanocytoma,* a central nervous system tumor showing mainly melanocytic features, can be difficult. Indeed, these two tumors may represent a lesion continuum. Melanocytomas typically arise in the cranial or spinal leptomeninges (Limas and Tio, 1972; Winston et al., 1987; Jellinger et al., 1988; Prabhu et al., 1993; Brat et al., 1999), are usually demarcated and compressive of their surroundings, and consist of often heavily pigmented, polygonal to somewhat elongate or dendritic cells with vesicular nuclei and distinct nucleoli. Mitoses are scant to absent. Although their immunoprofile is similar to that of pigmented schwannoma, staining for collagen type 4 is often less abundant. The differential may require electron microscopy. Features common to both tumors include pigmented melanosomes, occasional intermediate junctions, and basement membrane production. Not only are melanocytomas devoid of psammoma bodies and adipose-like cells, but in our experience, they ultrastructurally lack both pericellular basement membrane as well as long-spacing collagen.

The distinction of melanotic schwannoma from *metastatic melanoma* is, of course, crucial. In melanotic schwannomas of Carney's complex, this is easy, given the presence of psammoma bodies and adipose-like cells (Carney, 1990). The mean age for patients with such psammomatous melanotic schwannomas (PMS) and the complex is 22 years, a decade younger than ordinary melanotic schwannomas. In addition to PMS, the complex includes lentiginous pigmentation, blue nevi, myxomas of heart, skin or breast, congenital osteochondromyxoma, and endocrine overactivity (pigmented nodular adrenocortical disease with Cushing's syndrome, large cell Sertoli cell tumors of testis with sexual precocity, pituitary adenoma with acromegaly). Melanotic schwannoma is favored over melanoma if the tumor arises in ganglia; features fat and/or psammoma bodies; has cells with a dendritic appearance, benign or only slightly atypical cytology, and immunochemical or ultrastructural evidence of surface basement membrane production. The latter is rarely seen in melanoma (Dimaio et al., 1982; Prieto and Woodruff, 1998).

Clear cell sarcomas (soft tissue melanoma) (Enzinger, 1965; Chung and Enzinger, 1983) show a predilection for soft tissues, are macroscopically and microscopically invasive, and consist of cytologically malignant cells with little or no pigment. Psammoma bodies and fat are lacking, as is basement membrane formation.

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