Perineurioma
A Distinctive and Underrecognized Peripheral Nerve Sheath Neoplasm

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- **Context.**—Perineuriomas are benign peripheral nerve sheath neoplasms composed of perineurial cells with characteristic immunohistochemical and ultrastructural features. They have been traditionally classified into two main types according to their location—intraneural and extraneural—and overlap histologically with many other tumors, which may be diagnostically challenging to general surgical pathologists.

- **Objective.**—To review the clinical, morphologic, immunohistochemical, ultrastructural, cytogenetic, and molecular genetic aspects of perineurioma, as well as to discuss its clinicopathologic variants and differential diagnosis.

Described by Lazarus and Trombetta in 1978, perineurioma is an uncommon and underrecognized neoplasm defined as a peripheral nerve sheath tumor composed exclusively of neoplastic perineurial cells that demonstrate ultrastructural and immunohistochemical features similar to those of their normal cell counterpart. Normal perineurial cells constitute the perineurium, a protective barrier situated between the epineurium and endoneurium layers of the nerves that surround both myelinated and unmyelinated axon-Schwann cell complexes of peripheral nerve fascicles. The perineurium has direct continuity with the pia-arachnoid membrane of the central nervous system.

In contrast to other peripheral nerve sheath tumors, perineuriomas have not been found to be associated to neurofibromatosis. They mainly affect adults, but some cases have been described in children. Two main forms of perineurioma exist: intraneural and extraneural. Intraneural perineuriomas are restricted to peripheral nerve boundaries, while extraneural perineuriomas are found mainly in soft tissues and skin. Extraneural perineuriomas seem to be more common than intraneural perineuriomas, and although they usually have no connection to peripheral nerves, sometimes such an association may be apparent in small lesions. In some cases, extraneural perineuriomas and intraneural perineuriomas may contain residual entrapped Schwann cells, axons, and fibroblasts. On the basis of different clinical and pathologic characteristics, extraneural perineuriomas are further subclassified into soft tissue, sclerosing, and reticular (retiform) subtypes. It is important for pathologists to be familiar with the histopathologic features of perineuriomas so as to avoid getting confused with a variety of malignant mesenchymal tumors and, thereby, avert overly aggressive intervention.

The objective of this article is to review the clinicopathologic subtypes of perineurioma, highlighting their morphologic and immunohistochemical aspects and their main differential diagnoses. Ultrastructural, cytogenetic, and molecular genetic findings of perineuriomas are also reviewed.

**Clinicopathologic Variants**

**Extraneural Soft Tissue Perineurioma**

Extraneural soft tissue perineurioma (ESTP) is a benign peripheral nerve sheath neoplasm that often occurs in the subcutaneous tissues of the trunk and limbs as a painless, solitary nodule or mass. Less frequently, it can be restricted to the dermis or occur in deep soft tissues. Some examples have also been described in the head and neck area, retroperitoneum, brain, kidney, and intestines. Despite the initial observations suggesting that females were more frequently affected, more recent series have shown that ESTP has no sex or age predilection; it has been observed in both young children and older individ-
Extraneurial soft tissue perineurioma (ESTP). A, Macroscopically, ESTP is usually a well-circumscribed, whitish, and nonencapsulated neoplasm. B, Histologically, the neoplastic cells’ shape varies from plump and epithelioid (center to right) to elongated and wavy (bottom left) (hematoxylin-eosin, original magnification ×200). C, Characteristic ESTP spindle cells with tapering nuclei and long, thin, and widely separated cytoplasmic processes (hematoxylin-eosin, original magnification ×400). D, Ultrastructurally, the neoplastic perineural cells have elongated nuclei, margined chromatin, and the characteristic long and thin cytoplasmic processes (electron microscopy, original magnification ×10,600).

Macrosopically, the tumors are usually white to gray, are well circumscribed but not encapsulated, and have a firm consistency (Figure 1, A). Most cases range in size from 1.5 to 7 cm, but very large and very small examples measuring 20 and 0.3 cm, respectively, are on record. Histologically, ESTPs are composed of elongated neoplastic cells with wavy-shaped nuclei. However, their cytologic appearance varies; sometimes they are plumper and even epithelioid (Figure 1, B). Their cytoplasm shows slight eosinophilic features and indistinct cell boundaries (Figure 1, B). Characteristic spindle cells with tapering nuclei and elongated and extremely thin, widely separated bipolar cytoplasmic processes are found at least focally (Figure 1, C); these characteristic features can also be appreciated at the ultrastructural level (Figure 1, D). The cells may be disposed in varying manners, such as in a lamellar arrangement, perivascular whorling formation (Figure 2, A and B), or even short bundles with a vague storiform pattern reminiscent of that seen in dermatofibrosarcoma protuberans (Figure 2, C). The intercellular matrix may be abundant or scarce, which gives the lesion a hypocellular or hypercellular appearance, respectively (Figure 2, A and D). The stroma can vary from a more collagenous (Figure 3, A) to a more myxoid or loose appearance (Figure 2, A), and mixed collagenous-myxoid features can often be seen in the same lesion. Tissue cracking artifacts (Figure 3, B) and thick blood vessels (Figure 3, C) are also common. Mitotic figures and necrosis are usually absent, but in larger tumors central ischemic infarcts may be seen.

The classic immunohistochemical profile of ESTP includes positivity for epithelial membrane antigen (EMA) (Figure 3, D), collagen type IV, laminin, and vimentin and negativity for S100 protein. The pattern of EMA expression reflects the elongated bipolar cytoplasmic processes of the tumor cells and varies: it may be strong and diffuse in some cases or just focal and weak in others, so that its detection is possible only at high-power examination in some instances. Hornick and Fletcher have shown that up to 65% of the cases are positive for CD34, but other series have shown negative results for this antigen. The causes for these discrepant data are probably related to different anti-CD34 antibodies, immunohistochemical protocols, or inclusion criteria used in these studies.
Figure 2. Extraneural soft tissue perineurioma (ESTP). A and B, Hypercellular lesions showing the typical whirling architecture (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]). C, A vague storiform pattern is frequently found in ESTP (hematoxylin-eosin, original magnification ×200). D, Hypocellular areas with loose stroma may be present in some cases (hematoxylin-eosin, original magnification ×100).

Images in Figures 2, B and C, and 3, D, are from a 40-year-old man who presented with a 3.5-cm mass restricted to the subcutaneous adipose tissue of the left shoulder. The tumor was diffusely positive for epithelial membrane antigen, collagen type IV, and vimentin; focally positive for CD34 and laminin; and negative for S100 protein and smooth muscle actin. Figures 2, D, and 1, C, are representatives of a soft tissue mass that showed similar immunoprofile. This lesion was situated in the hand of a 60-year-old man.

Although several ESTPs are negative for pan-cytokeratins, the expression of cytokeratins has not been widely studied in ESTP. Since their expression has already been detected in perineurial cells of pigs, in meningiomas, in sclerosing perineuriomas, and in reticular perineuriomas, the expression of cytokeratins in at least a subset of ESTP would not be surprising.

Depending on location, ESTPs may mimic other lesions (Table). For those occurring in the superficial locations, the differential diagnosis mainly includes dermatofibrosarcoma protuberans (DFSP), soft tissue meningioma, and myxofibrosarcoma (Table). Dermatofibrosarcoma protuberans grows in a more diffuse storiform pattern, spreading along subcutaneous connective septa and adipose tissue with the characteristic honeycomb pattern. Most DFSPs are diffusely negative for EMA; however, DFSP may rarely express EMA, which can be a diagnostic challenge. In such instances, molecular methods can help because DFSP is characterized by the presence of supernumerary ring chromosomes containing the (17;22), which leads to the formation of the fusion gene COL1A1-PDGFB. The cytogenetic abnormality can be detected by using conventional cytogenetics on fresh tissues and fluorescent in situ hybridization or reverse transcriptase polymerase chain reaction on paraffin-embedded tissues. The cytogenetic and molecular genetic findings of perineuriomas are discussed later in this article.

The distinction between soft tissue meningioma and perineurioma is quite difficult and of little clinical value. Since perineurial cells and arachnoid cap cells (from which meningioma derives in the central nervous system) share significant morphologic and immunohistochemical similarities, both neoplasms have similar morphologic and immunohistochemical features. However, there may be some subtle differences at the ultrastructural level (eg, meningioma lacks pinocytotic vesicles). Moreover, because normal perineurial cells are continuous with the arachnoid membrane cap cells at the intervertebral foramina, some authors view perineurioma as the peripheral counterpart of meningioma.

For deep-seated perineuriomas, the differential diagnosis mainly includes desmoid-type fibromatosis, low-
grade fibromyxoid sarcoma (LGFS), solitary fibrous tumor, low-grade leiomyosarcoma, leiomyoma, and myxofibrosarcoma (Table). We emphasize here the distinction of ESTP from desmoid-type fibromatosis, LGFS, and solitary fibrous tumor. The other elements of the differential diagnosis can be found in the Table. Fibromatosis is best distinguished by its long fascicles composed of spindle cells with tapering or plump vesicular nuclei, depicting a more homogeneous and dense collagenous matrix, and by diffuse expression of smooth muscle actin and muscle-specific actin; these proteins are usually more focally detected in perineuriomas.\textsuperscript{14,24}

Low-grade fibromyxoid sarcoma is a particularly difficult differential diagnosis since it may have overlapping histologic features with perineurioma. In contrast to this, LGFS exhibits alternation of more myxoid zones with more collagenous zones with arcade vessels, and occasionally giant collagen rosettes. Epithelial membrane antigen immunoeexpression has been noticed in these tumors.\textsuperscript{25} In difficult cases, one can rely on cytogenetics or molecular genetic analysis using reverse transcriptase polymerase chain reaction to detect, respectively, the translocation \(t(7;16)(q32\rightarrow p11)\) or its fusion product \(FUS/CREB3L2\) in LGFS.

In contrast to ESTP, solitary fibrous tumor is composed of bland ovoid-shaped to spindle-shaped cells without the cytologic features of perineurioma, arranged in the so-called patternless pattern, and has blood vessels often showing a hemangiopericytoma-like branching. Immunohistochemically, most solitary fibrous tumors are EMA negative and CD34 positive; however, a subset of cases may show focal EMA expression, which may cause difficulties in the differential diagnosis.\textsuperscript{26}

Other differential diagnoses include benign peripheral nerve sheath tumors, such as schwannoma and neurofibroma. However, most cases can be easily differentiated at the morphologic level. In difficult cases, immunohistochemistry is helpful because S100 protein expression is rarely found in perineuriomas.\textsuperscript{9,14} Of note, similar to the concept of peripheral nerve sheath tumors with mixed schwannoma-neurofibroma features,\textsuperscript{27} benign peripheral nerve sheath tumors with hybrid features of perineurioma-neurofibroma and perineurioma-schwannoma have been recently recognized in small series by Zamecnik and
**Perineuriomas and Their Potential Differential Diagnoses**

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<td>Fibromatosis: Long fascicles, spindle cells with tapering or plump vesicular nuclei, dense collagenous matrix, infiltrative growth pattern, and slitlike vessels; diffuse expression of smooth muscle actin and muscle specific actin</td>
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<td>Smooth muscle tumors: Blunt-ended nuclei, abundant eosinophilic cytoplasm, intersecting fascicles; positivity for smooth muscle actins (diffuse) and desmin</td>
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<td>LGFMS: Alternated myxoid/collagenous zones, arcade vessels, giant collagen rosettes; immunohistochemistry not helpful; t(7;16)(q32→p11) with the fusion gene FUS-CREB3L2</td>
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<td>Solitary fibrous tumor: Patternless pattern with dense collagen bundles, hyalinized vessels, staghorn vessels, focal storiform pattern may be present; most are EMA negative and CD34 positive</td>
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<td>Low-grade myxofibrosarcoma: Higher degree of cytologic atypia and pleomorphism, cells with cytoplasmic inclusions (pseudo-lipoblasts), curvilinear and thin blood vessels, whorling growth pattern unusual; EMA negative</td>
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<td>Schwannoma: Antoni A and Antoni B areas, Verocay bodies; diffuse S100 expression</td>
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<td>Neurofibroma: Spindle cells with wavy nuclei and poorly defined, slightly eosinophilic cytoplasm and several small nerve twigs embedded in a variably fibromyxoid matrix; extensive S100 expression; often CD34 positive</td>
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<td>Fibroma of tendon sheath: Associated with tendons, more deeply situated; spindled fibroblasts in a collagenous stroma, no epithelioid and plump cells arranged in linear or corded pattern; slitlike vessels; EMA negative</td>
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<td>Epithelioid glomus tumor: Cells have abundant cytoplasm, form clusters around blood vessels; diffuse expression of muscle-specific and smooth muscle actins; EMA negative</td>
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<td>Sclerosing peri-</td>
<td>Giant cell tumor of tendon sheath: Deep-seated; admixture of mononuclear histiocytic, xanthomatous, and osteoclast-like giant cells, tendency of nested growth; CD68 positive, focal desmin positive or negative; abnormalities in chromosome 1 with clustering in the p11→13 region</td>
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<td>neuriuma</td>
<td>Epithelioid sarcoma: Higher nuclear atypia, cells disposed in micronodules that show central necrosis and perineurial and vascular invasion; immunohistochemistry: cytokeratin positive, CD34 positive in 50%–70% of cases</td>
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<td>Myxoid MPNST: Nuclear atypia, mitotic figures, perivascular hypercellularity and tumor necrosis, no reticular architecture; immunohistochemistry less useful, but positivity for S100 and negativity for EMA may help</td>
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<td>Myxoid synovial sarcoma: Greater nuclear atypia and higher mitotic index, fascicular spindle cell areas; immunohistochemistry: EMA and cytokeratin positive; translocation t(X;18)(p11.2;q11.2) with the formation of the fusion transcripts SYT-SSX1 and SYT-SSX2</td>
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<td>Localized hypertrophic neuropathy: Onion bulb–like whorls result from Schwann cell (not perineurial cell) proliferation that encircles axon units</td>
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ESTP indicates extraneural soft tissue perineurioma; DFSP, dermatofibrosarcoma protuberans; EMA, epithelial membrane antigen; LGFMS, low-grade fibromyxoid sarcoma; GFAP, glial fibrillary acidic protein; and MPNST, malignant peripheral nerve sheath tumor.

*Michal and by Michal et al.*, respectively. Other groups have encountered similar findings, and these neoplasms have been characterized morphologically, immunohistochemically, and in some examples ultrastructurally. They have a predilection for the skin and subcutaneous tissues of the trunk and upper extremities, and, in contrast to hybrid schwannoma-neurofibroma tumors, so far no cases have shown association with neurofibromatosis. Perhaps the most reasonable hypothesis for the divergent differentiation seen in peripheral nerve sheath neoplasms is their origin from a pluripotential precursor mesenchymal tissue or cell.

**Sclerosing Perineurioma**

Sclerosing perineurioma is an extraneural soft tissue perineurioma variant first described by Fetsch and Miettinen, who reported 19 tumors, all arising in the hands, mainly of young male adults. Although ordinary ESTP outnumbers published cases of sclerosing perineurioma, the latter seems to be more common than the former in some institutions. However, a direct comparison between the frequencies of these two subtypes has not yet been established in the literature. Sclerosing perineurioma examples are well circumscribed and unencapsulated, have firm consistency, and are small (usually 3 cm or less in diameter). Microscopically these tumors may involve the dermis (Figure 4), dermis and subcutis simultaneously, or...
The neoplastic cells are embedded in a prominent collagenous stroma; they are disposed in a corded pattern, sometimes swirling around small blood vessels (hematoxylin-eosin, original magnification ×40). A discrete perivascular whorling pattern is seen in this field (hematoxylin-eosin, original magnification ×100). C, Neoplastic cells intermixed with collagenous stroma and an entrapped small nerve twig are barely seen at the bottom right (hematoxylin-eosin, original magnification ×200). The tumor shown in A was located in the palmar aspect of a 59-year-old man’s hand. B and C illustrate a lesion situated in the right ring finger of a 33-year-old man. (Courtesy of Antonio G. Nascimento, MD, from Mayo Clinic, Rochester, Minn [A] and Emilio M. Pereira, MD, Laborarorio Salomao e Zoppi, Sao Paulo, Brazil [B and C].)

The differential diagnosis for sclerosing perineurioma mainly includes fibroma of tendon sheath, epithelioid glomus tumor, epithelioid sarcoma (Table), and highly collagenized examples of giant cell tumor of tendon sheath. Fibroma of tendon sheath is deeper seated than sclerosing perineurioma and is EMA negative. Glomus tumor differs from sclerosing perineurioma in that glomus cells have more abundant cytoplasm and diffusely express actins but not EMA. Giant cell tumor of tendon sheath frequently occurs in the fingers; some cases are extensively collagenized and may pose morphologic difficulties to the differential diagnosis with sclerosing perineurioma. However, giant cell tumor of tendon sheath is EMA negative as well.

Reticular (Retiform) Perineurioma

Reticular (retiform) perineurioma is a rare extraneural perineurioma variant with few examples reported in the...
Microscopically, most tumors are surrounded by a hypocellular pseudocapsule, but some examples have shown just ill-defined, parallel bundles of perineurial cells surrounding nearly indistinguishable nerve fibers characteristic of transverse sections. Instead, longitudinal sections may pose diagnostic difficulties because they do not depict the pseudo–onion bulb pattern characteristic of cross sections of the affected nerve (Figure 7, B) containing spindled perineurial cells arranged in pseudo-onion bulb–like whorls (Figure 6). Mitotic figures, necrosis, and hemorrhage are usually not identified, although focal slight nuclear atypia and nuclear hyperchromasia may be seen in some cases. The myxoid stroma demonstrates microcystic changes, and areas of stromal hyalinization may be seen. The vasculature is predominantly composed of small capillary-size blood vessels, but occasional large or ectatic vessels are also found within the lesion. Immunohistochemically, most reticular perineuriomas diffusely express EMA and are negative for S100 protein and smooth muscle actin; a subset of cases show focal expression of CD34, desmin, cytokeratin (AE1/AE3), and pan-cytokeratin (MNF116).11

The differential diagnosis mainly includes myoepithelial tumors, myxoid malignant peripheral nerve sheath tumor (MPNST), and myxoid synovial sarcoma (Table). Myoepithelial lesions may have histologic features similar to those of reticular perineurioma, but they often contain an acinar or ductal component and have a different immunophenotypic profile characterized by variable positivity for S100 protein, cytokeratins, glial fibrillar acidic protein, and smooth muscle actin.39

In contrast to reticular perineurioma, MPNST frequently demonstrates substantial nuclear atypia, significant mitotic figures, perivascular hypercellularity, and tumor necrosis. The reticular architecture is generally not seen in MPNST. Immunohistochemical studies are less useful in the distinction between these entities because MPNST may exhibit perineurial differentiation.40 About one half of the cases of MPNST demonstrate focal S100 protein positivity, and they are usually EMA negative.41

Synovial sarcoma with extensive myxoid changes can be differentiated from reticular perineurioma by focal spindle cell areas, greater nuclear atypia, and higher mitotic index. Within this morphologic context, EMA and cytokeratin positivity, as well as the frequent CD99 and Bcl-2 protein expression, point toward the correct diagnosis. In doubtful cases, molecular techniques may be of help, since cytogenetic procedures and reverse transcriptase polymerase chain reaction are able to detect, respectively, the translocation t(X;18)(p11.2;q11.2) and the corresponding most common chimeric fusion transcripts SYT-SSX1 and SYT-SSX242 in synovial sarcomas.

Intraneural Perineurioma

Intraneural perineurioma is a benign neoplasm composed exclusively of perineurial cells restricted to the boundaries of a nerve. This term was proposed by Emory et al10 to combine lesions previously classified as localized hypertrophic neuropathy, hypertrophic mononeuropathy, localized hypertrophic neurofibrosis, intraneural neurofibroma, and hypertrophic interstitial neuritis. Intraneural perineurioma primarily affects the extremities of young adults and children, in whom it produces a fusiform expansion of a major nerve (Figure 7, A) with associated motor deficiency and occasional sensory loss. With exception of a case involving the spinal roots of both C8 and T1,2 the process is limited to a single nerve. It has rarely been described in unusual sites43 and in smaller, unnamed nerves.39,44 When occurring in such small nerves, no motor-sensory disturbances may be clinically apparent. Histologic examination of a cross section of the affected nerve shows irregularly enlarged, hypercellular nerve fascicle (Figure 7, B) containing spindled perineurial cells arranged in pseudo-onion bulb–like whorls around one or more centrally situated Schwann cell and axons in varying stages of degeneration (Figures 7, C, and 8, A). Longitudinal sections may pose diagnostic difficulties because they do not depict the pseudo–onion bulb pattern characteristic of transverse sections. Instead, longitudinal sections show just ill-defined, parallel bundles of perineurial cells surrounding nearly indistinguishable nerve fibers (Figure 8, B). Immunohistochemistry reveals EMA-positive perineurial cells arranged in the pseudo–onion bulb whorls (Figure 8, C) around EMA-negative, S100-positive...
Schwann cells accompanying axonic structures.\textsuperscript{22} It should be differentiated from localized hypertrophic neuropathy (Table), an entity that, as defined by Scheithauer et al.,\textsuperscript{9} is most likely a reactive condition that affects peripheral nerves, being characterized by nerve fascicle expansion due to the formation of onion bulb–like whorls of uniform S100-positive and EMA-negative Schwann cells (not perineurial cells as in intraneural perineurioma) encircling a variably myelinated axon.\textsuperscript{9,45}

The nature of intraneural perineurioma had been a subject of debate,\textsuperscript{46–48} but the recent identification of clonal cytogenetic abnormalities in these lesions by Emory et al\textsuperscript{2} has confirmed its neoplastic nature.

**ARE THE PERINEURIOMA VARIANTS INDEED DIFFERENT PRESENTATIONS OF THE SAME ENTITY?**

According to some authors, perineurioma variants (ESTP, sclerosing perineurioma, reticular perineurioma, and intraneural perineurioma) can be viewed as part of a spectrum of different presentations of the same entity. Their similar ultrastructural features and the occurrence of rare cases with histopathologic features of more than one subtype\textsuperscript{13,38} support this impression. However, preliminary data suggest that there may be different genetic mechanisms for some of the perineurioma subtypes (see following section on cytogenetics and molecular genetics),\textsuperscript{7,49} which consequently may have a different pathogenesis. Thus, at the present time, there is some uncertainty as to whether the 4 subtypes of perineurioma are indeed different presentations of the same entity.

Interestingly, other extremely rare histopathologic perineurioma variants have been reported, including perineurioma with granular cells,\textsuperscript{50} perineurioma with ossification,\textsuperscript{51} perineurioma with adipocytes,\textsuperscript{52} plexiform perineurioma,\textsuperscript{36} and the controversial cutaneous sclerosing Pacinian-like perineurioma.\textsuperscript{53}

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**ELECTRON MICROSCOPY AND IMMUNOHISTOCHEMISTRY**

In 1978, Lazarus and Trombetta\textsuperscript{1} described the first case of perineurioma in the soft tissues of the calf of a 45-year-old man, based on the ultrastructural similarity between the neoplastic cells to the normal perineurial cells, whose features include the presence of elongated, tapered nuclei with delicate chromatin; long thin cytoplasmic processes with pinocytotic vesicles; cell envelopment by basal lam-
Figure 8. Intraneural perineurioma. A, Pseudo-onion bulbs are composed of perineurial neoplastic cells surrounding 1 or more nerve fibers and Schwann sheaths (hematoxylin-eosin, original magnification ×400). B, Longitudinal section of the affected nerve displays parallel and ill-defined perineurial cells around nearly indistinguishable nerve fibers (hematoxylin-eosin, original magnification ×100). C, Epithelial membrane antigen expression by perineurial cells encircling negative nerve fibers and their accompanying Schwann sheaths (immunohistochemistry, original magnification ×400). (Courtesy of Bernd W. Scheithauer, MD, Mayo Clinic, Rochester, Minn.)

ina; and the presence of intercellular junctions, including tight junctions (Figure 1, D). Since then, electron microscopy has been considered the gold standard technique in confirming the diagnosis of perineurioma and its different variants.

With the advent of immunohistochemistry, Pinkus and Kurtin, in 1985, were the first to note EMA expression in perineurial cells. Epithelial membrane antigen is an incompletely characterized antigen that is found in a group of carbohydrate-rich, protein-poor, high-molecular-weight molecules detected on the surface of many types of epithelia. After Pinkus and Kurtin’s article, many other reports have shown EMA expression in perineuriomas, turning this marker into an important adjunct in differentiating perineurioma from its morphologic mimickers. Nevertheless, the use of EMA as a perineurial marker presents some drawbacks. First, the cytoplasmic processes of perineurial cells are extremely thin and widely separated, and EMA reactivity may be difficult to demonstrate without using higher antibody concentrations or longer incubation times than routinely employed in the diagnosis of epithelial neoplasms; even when these precautions are taken, sometimes EMA positivity may be focal and weak. The literature contains examples of ultrastructurally well-documented EMA-negative perineuriomas. Second, EMA expression in soft tissue neoplasms is not restricted to perineuriomas; it can be detected in neoplasms with (myo)fibroblastic differentiation as well as in synovial sarcomas, epithelioid sarcomas, and in other mesenchymal neoplasms. To diminish these problems, two additional protein markers have recently been reported to be helpful in confirming the diagnosis of perineurioma: claudin-1 and human erythrocyte glucose transporter-1 (GLUT-1).

Claudins are a group of 20 homologous transmembrane proteins, of which claudin-1 and claudin-2 were identified as the main integral components of tight junctions in epithelial and endothelial cells. Recent studies have shown expression of different claudin proteins in solid tumors, such as ovarian carcinoma and synovial sarcomas. Folpe et al evaluated the expression of different tight junction-associated proteins in nonneoplastic soft tissues, and realized that claudin-1 antibody consistently detected perineurial cells of normal nerves but not other
Mesenchymal tissues. The explanation for this finding resides in the fact that normal and neoplastic perineurial cells contain tight junctions.\textsuperscript{63} Such finding lead Folpe et al\textsuperscript{62} to evaluate the expression of claudin-1 in perineuriosas; they found that up to 92\% of their cases were positive for claudin-1, and that its membrane pattern of expression was stronger and more diffuse in a given perineuriosia case than was EMA expression. Interestingly, other neoplasms with fibroblastic/myofibroblastic differentiation evaluated by these authors (DSFP, LGFS, desmoplastic fibrobl astoma, and fibromatosis) did not express this antigen. Claudin-1 was detected focally in presumably peri-broblastoma, and fibromatosis) did not express this anti-plasms with fibroblastic/myofibroblastic differentiation.

Cytogenetic studies have shown that both intraneural and extraneural perineuriosas show chromosome 22 abnormalities, mainly monosomy or deletion of the 22q11\textendash{}q13.1 bands.\textsuperscript{2} Deletions and point mutations of the NF\textsubscript{2} gene on 22q12 are frequently found in perineuriosas, but this finding can be seen in schwannomas and several other solid tumors.\textsuperscript{49,67} Recent studies have shown that chromosome 10q rearrangements or deletions seem to be a recurrent abnormality in sclerosing perineuriosas.\textsuperscript{7} An isolated case of ESTP with loss of the chromosome 13 has also been reported.\textsuperscript{68}

**Prognosis**

Conventional extraneural perineuriosas have thus far followed a benign clinical course, and surgical resection with margins free of neoplasm is typically curative, regardless of subtype. However, malignant perineuriosia (also known as MPNST with perineurial differentiation or perineurial MPNST) has recently been recognized as a rare variant of MPNST.\textsuperscript{40,69} Hirose et al\textsuperscript{40} reported 7 MPNSTs with perineurial differentiation situated in the subcutis of extremities and in the trunk and face, and visceral lesions involving the mediastinum and retroperitoneum of adults. None were associated with neurofibromatosis, and only 1 was associated with a nerve. As with conventional ESTP, the tumors were composed of spindle cells showing elongated and thin bipolar cytoplasmic processes, arranged in intersecting fascicles, whorls, or stori-form pattern, sometimes forming perivascular whorls; they were embedded in a variable amount of intercellular stroma. However, malignant histologic features were also detected. Four cases were classified as high-grade by showing tumoral necrosis, exuberant cytologic atypia, or numerous mitotic figures. Three cases were labeled as low-grade malignant (see following discussion). All cases were S100 protein negative and EMA positive and showed ultrastructural features of perineurial differentiation. Malignant perineuriosia is very rare, and its diagnosis may be difficult without confirmatory ultrastructural studies\textsuperscript{61} because EMA positivity is also seen in other high-grade spindle cell sarcomas (eg, epithelioid sarcoma and monophasic synovial sarcoma), as well as in spindle cell squamous cell carcinoma. Although claudin-1 and GLUT-1 have not been widely studied in malignant perineuriosas, Hirose et al\textsuperscript{60} showed that GLUT-1 may be helpful in confirming this diagnosis. In the first series on malignant perineuriosia written by Hirose et al,\textsuperscript{60} the authors suggested that this tumor would probably be less aggressive than the conventional MPNST, but the number of cases published so far is too limited to allow definitive conclusions.

The concept of “low-grade malignant perineuriosia” was first introduced by Hirose et al.\textsuperscript{69} These authors found that 3 of their malignant perineuriosas differed from the conventional perineuriosas by showing scattered cytologic atypia, infiltrative growth pattern, and higher mitotic activity. At the same time, these lesions did not fit the histologic criteria of malignancy found in the high-grade malignant perineuriosia. Since none of these cases developed distant metastasis during follow-up periods that ranged from 55 to 75 months, the authors labeled such lesions as low-grade malignant perineuriosas, but they recognized the possibility that these neoplasms could represent “atypical” or “cellular” perineuriosas. Hornick and Fletcher\textsuperscript{14} reported 14 perineuriosas with atypical features in their series, 10 of which had clinical follow-up ranging from 12 to 134 months. In this series, the low-grade atypical features included scattered pleomorphic cells, abrupt transition from typical morphology to a markedly hypercellular area with cytologic atypia, and diffuse infiltration of skeletal muscle by tumor cells; of the 10 cases with such features, only 1 recurred locally, but no case metastasized. On the basis of their findings, Hornick and Fletcher\textsuperscript{14} suggested that perineuriosas with such features probably would be better called typical perineuriosas instead of low-grade malignant perineuriosas. Nevertheless, one example of perineuriosia with low-grade features that behaved in a malignant fashion (with multiple distant metastases) 10 years after the initial presentation is on record.\textsuperscript{70} Moreover, only a few examples of such kind of tumor have been described so far and, even though most of those reported cases behaved in a benign fashion,
limited follow-up periods are available in most reports.\(^7\)\(^{–}\)\(^7\)\(^3\) If one recalls that low-grade malignant mesenchymal neoplasms may take more than 10 years to metastasize, it becomes clear that additional follow-up is needed before the true potential of these tumors is known. As a result, the term perineurioma of uncertain malignant potential could also be used for cases with atypical but not overtly malignant features.

Intraneural perineurioma is a benign neoplasm, but its treatment is controversial. Put simply, in an attempt to preserve nerve function, some authors advocate diagnostic biopsy followed by neurolysis instead of resection,\(^2\) while others prefer the resection with neural grafting or end-to-end anastomosis because, according to them, intraneural perineurioma is a progressive condition that evolves inexorably to a total loss of nerve function.\(^7\)\(^4\)

**CONCLUSION**

Perineurioma is an uncommon and underrecognized benign neoplasm that exhibits histologic features that overlap with those of many other benign and malignant soft tissue tumors. The correct diagnosis relies mainly on histologic findings and immunohistochemical profile, but ultrastructural studies can be used in difficult cases. Cytogetic and molecular genetic studies are still of limited value for the diagnosis of perineuriomas but may play a fundamental role in excluding important differential diagnostic considerations, such as DFSP and low-grade fibromyxoid sarcoma.

**Note.** In this article we state that perineuriomas have never previously been associated with neurofibromatosis. However, after our article was accepted for publication, an article describing the occurrence of a soft tissue perineurioma in the clinical setting of neurofibromatosis type 2 was published. The reference for this recent article is Pitchford CW, Schwartz HS, Atkinson JB, Cates JM. Soft tissue perineurioma in a patient with neurofibromatosis type 2: a tumor not previously associated with the NF2 syndrome. Am J Surg Pathol. 2006;30:1624–1629.

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