The majority of tumors affecting the peripheral nerve are nerve sheath tumors. Most are derived from and consist largely, if not entirely, of Schwann cells. These lesions include histological variants of schwannomas and neurofibromas. Tumors of perineurial cells are far less common, although perhaps least frequent are mesenchymal tumors originating in the epineurium. Among these epineurial lesions, benign examples include hemangioma, angiomatosis, paraganglioma, lipoma, and meningioma as well as such oddities as hemangioblastoma, adrenal adenoma, and glomus tumor. Intraneural glomus tumors are rare. To our knowledge, only 6 cases involving nerves of various sizes have been reported. Glomangioma, a variant of glomus tumor that can resemble a hemangioma because of its increased number of vessels, is even less common. Herein, we describe the clinicopathological features of a large, very long-standing glomus tumor involving the left sciatic nerve and a glomangioma of the left median nerve. The literature is also reviewed.

Case Reports

Case 1

History. This 32-year-old man had a 2-year history of left lower-extremity radicular pain extending down the back of the leg to the dorsomedial aspect of the left foot. That pain had recently subsided and was followed by a 4-month history of burning sensation affecting the left ankle and foot. On taping the left ankle, his coach confirmed his inability to raise the left foot. This weakness has persisted to the present.
Dullness in the left posterior thigh. The range of motion in the extremities was full and pain free. However, thigh and calf circumferences were smaller on the left side than on the right (47 cm compared with 49 cm, and 36.7 cm compared with 39.5 cm, respectively), and decreased muscle tone was noted in the left foot. Power was MRC Grade 5/5 in all 4 extremities except for left foot and toe dorsiflexion, which were MRC Grade 1/5. There was also decreased sensation in the left S-1 distribution. Deep tendon reflexes were 1+ and equal in the upper extremities, at both knees, and in the right ankle but were absent in the left ankle. Equivocal plantar responses were noted bilaterally. A high-stepping gait was evident on the left side. Sensory examination revealed hypesthesia over the dorsomedial left foot.

Routine laboratory tests were nondiagnostic. Electromyography, nerve conduction studies, and an H-reflex study were all compatible with a left sciatic neuropathy with dysfunction distal to the branch innervating the short head of the biceps femoris muscle. The dysfunction was greater in the peroneal trunk. An MR image (Fig. 1A) revealed a 7.0 × 2.8 × 1.6-cm fusiform mass within the left sciatic nerve beginning 22 cm distal to the midfemoral head and 11 cm distal to the greater trochanter. The mass was heterogeneous with areas of increased T2 signal and mild to moderate enhancement throughout.

Operation. The patient underwent left midthigh surgical exploration and subtotal resection (40%) of the tumor for nerve decompression. Intraoperatively, the tumor was oblong in shape with moderate vascularity, partial infiltration, and adherence of sciatic nerve fascicles mainly in the central portion of the lesion (Fig. 1B).

Pathological Analysis. A 1.5-cm-long and 0.3-cm-diameter nerve fascicle was grossly unremarkable; an intraoperative biopsy specimen showed no microscopic abnormality. A frozen section of the tumor revealed an epithelioid-appearance lesion suggestive of an epithelioid schwannoma. An irregular specimen measured 1.2 × 0.3 × 0.3 cm and was soft, hemorrhagic to yellow in appearance, and not associated with visible nerve tissue. Microscopically, the tumor was cellular, featured diffuse sheet-like growth and thin-walled gaping vessels, and was histologically uniform and cytologically monomorphic (Fig. 2A). The rather epithelioid tumor cells were round to oval in contour, showed well-demarcated cell membranes, and exhibited relatively uniform round to minimally pleomorphic nuclei with frequent nuclear cytoplasmic inclusions and small nucleoli. No spindle cell element was seen. Maximal mitotic activity was 2 mitoses/50 hpf (magnification × 40; Fig. 2B). Microscopic infiltration of nerve fascicles was noted (Fig. 2C and D) despite a gross description of largely interfascicular growth. The MIB-1 labeling index was 5.2%. Immunohistochemistry (streptavidin-biotin-peroxidase complex method) utilizing antibodies directed toward SMA (clone 1A4, dilution 1:150, Dako), collagen IV (clone CIV22, dilution 1:25, Dako), CD117 (c-Kit, polyclonal, dilution 1:1000, MACH 3, Biocare Medical), p53 (clone DO-7, dilution 1:2000, Dako), and Bel-2 (clone 124, dilution 1:100, Dako) were positive (Fig. 3). In contrast, S100 protein (polyclonal, dilution 1:800, Dako), EMA (clone E29, dilution 1:20, Dako), pankeratin (clone AE1/AE3, dilution 1:200, Zymed), synaptophysin (SY38, dilution 1:40, ICN Biomedicals), glial fibrillary acidic protein (polyclonal, dilution 1:800, Dako), CD34 (My10, Becton Dickinson), CD99 (MIC2, clone 12E7, dilution 1:50, Dako), HMB45 (clone HMB-45, dilution 1:100, Dako), and MART-1 (clone M2-7C10, dilution 1:100, NeoMarkers) were negative. Neurofilament protein (clone 2F11, dilution 1:75, Dako) highlighted overrun axons (Fig. 2D). Electron microscopy performed on tissue deparaffinized, routinely processed, Epon-embedded, and stained with uranyl acetate and lead citrate disclosed cells with ample cytoplasm and well-demarcated borders with electron-dense substance between cells. Long-spacing collagen, abundant intracytoplasmic filaments, and occasional dense bodies were also present (Fig. 4). A benign glomus tumor was diagnosed despite the size of the lesion and the finding of nerve fascicle invasion.

Postoperative Course. Postoperatively, the patient’s symptoms markedly improved. He is neurologically stable.
and there has been no recurrence of his radicular pain at 11 months after resection.

Case 2

History and Examination. This 31-year-old man presented with a 3-year history of progressive left-hand weakness and forearm atrophy. Specifically, he noted an inability to flex his thumb and index finger, and he experienced numbness in the tips of these digits associated with burning pain at the base of the thumb.

Examination disclosed a severe but incomplete proximal median neuropathy with near paralysis of the flexor pollicis longus muscle, flexor digitorum profundus muscle to the index finger, and flexor carpi radialis muscle. In addition, the pronator teres muscle, flexor digitorum profundus muscle to the middle finger, and the thenar muscle were severely weak, whereas flexor digitorum superficialis and palmaris longus muscles were only mildly weakened. Two-point sensation in the radial 3 and one half digits was preserved, although sensation was subjectively decreased on the volar aspect of the thumb and index finger. Percussion tenderness over the median nerve was present several centimeters proximal to the antecubital fossa. Electromyography demonstrated a primarily axonal disorder affecting the median nerve proximal to the pronator teres muscle, most severely affecting the anterior interosseous nerve branch. Motor components of the nerve were more affected than its sensory components. A quantitative sensory examination showed heat-pain hypersensitivity in the hand. An MR image revealed a focally enlarged segment of the distal median nerve approximately 6 cm in length at the level of the medial condyle, which avidly enhanced (Fig. 5A and B). Profound atrophy of the median-innervated forearm muscles was also noted.

Operation. Exploration of the median nerve in the distal arm revealed a purple, vascular-appearing mass within a fascicle (Fig. 5C). The fusiform lesion measured ~ 2.5 cm

![Figure 2. Case 1. Photomicrographs depicting histopathological features. A: Prominent vessels and sheets of monotonous cells with eosinophilic cytoplasm and well-defined cell borders. H & E, original magnification × 200. B: Low-level mitotic activity. H & E, original magnification × 400. C: Tumor was intimately admixed with nerve and demonstrated prominent infiltration within and around nerve fascicles. H & E, original magnification × 200. D: Nerve infiltration confirmed by a neurofilament immunohistochemical stain, which highlights overrun axons. Original magnification × 200.]

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in length and was separable from the main median nerve (Fig. 5D). No epineurial or surface hypervascularity of the nerve was apparent. Because stimulation of this abnormal part of the nerve produced no muscle contraction, the portion was resected.

Pathological Analysis. The tumor was limited to a fascicle and formed an ovoid, very discrete, partially encapsulated 0.6 × 0.4 × 0.4–cm mass (Fig. 6A and B) associated with an adjacent 0.2-cm traumatic neuroma (Fig. 6C). Most of the tumor was cellular and composed of uniform arborizing sheets of demarcated, round to oval cells separated by small, often gaping vessels. Their nuclei had a similar configuration and featured delicate chromatin and occasional small nucleoli. Spindle cells were rare. Scattered mast cells were evident. Only a rare mitotic figure was found, and the MIB-1 labeling index was 1.8%. A somewhat minor part of the tumor had an angioma-like appearance with medium-caliber, thicker-walled vessels among which tumor cells were scant. Immunostains for vimentin and SMA were strongly positive (Fig. 6D), whereas keratin, EMA, and desmin preparations were negative. Staining for p53 was moderately immunopositive, and there was patchy labeling for Bcl-2 in tumor cells along with associated inflammatory cells. Neurofilament and S100 protein reactivity was limited to disorganized nerve fibers of the paratumoral traumatic neuroma.

Postoperative Course. Postoperatively, the patient noted no new neurological deficit. Given the long period of denervation, no nerve graft was performed. He remains well 7 months after surgery. His neurological function has remained unchanged, but the pain in the hand and elbow have resolved. He is considering tendon transfer to help with thumb flexion.

Discussion

It was Masson who first described glomus tumors, considering them hyperplastic glomus bodies. Composed of modified smooth-muscle cells, they are now recognized as neoplastic in nature. Normal glomus bodies represent arteriovenous anastomoses subserving thermal regulation. Nearly all of these lesions lie in the deep dermis, appear
dusky red, and consist in part of afferent arterioles with accompanying smooth-muscle cells and internal elastic laminae. Anastomoses of the latter with collecting veins take the form of Sucquet–Hoyer canals composed of plump endothelial-lined vessels with both circumferential and longitudinal smooth muscle ensheathment and the absence of an elastic lamina. The entire complex, replete with small unmyelinated nerve fibers, is surrounded by a collagenous capsule.

Glomus tumors are relatively common, representing nearly 2% of soft-tissue tumors. They occur primarily in young adults and show a marked female predominance. They are associated with constant or episodic, often shooting pain unresponsive to conventional therapies. The pain can be interrupted by stopping afferent blood flow, the basis of the tourniquet test. Pressure tenderness and cold hypersensitivity complete the diagnostic triad. Approximately 10% of glomus tumors occur in multiples. Such lesions are unencapsulated and less often associated with pain and tend to occur primarily in children and at unconventional sites. A rare association of glomus tumor with neurofibromatosis Type I has been described.

Glomangiomas occur less frequently than typical glomus tumors, show less tendency to circumscription, and most often involve the hand and forearm. Its gross and histological appearance is similar to that of cavernous hemangiomas except for the characteristic glomus cell aggregates between vessels. "Glomangiomyoma," the term given to a...
glomus tumor or glomangioma in which the cells transition to spindle cells with morphological features of smooth muscle, is even less common. Very few spindle cells were observed in the glomangioma in the present case.

Glomus tumors are only rarely malignant, with less than 50 cases having been reported to date. Approximately 25% of these lesions metastasize. Such tumors are defined on the basis of a large size (> 2 cm), a deep location, nuclear atypia including pleomorphism and prominence of nucleoli, a tendency to exhibit spindle or round cell features resembling fibro- or leiomyosarcoma on the one hand or Ewing sarcoma on the other, and increased mitotic activity (> 5 mitoses/50 hpf). Immunohistochemical features associated with malignancy include high-level reactivity for MIB-1, p53, and Bcl-2 as well as CD34. Malignant glomus tumors often possess a benign element as well. By size and location, the lesion in Case 1 meets the criteria for malignancy, and its infiltration of nerve fascicle(s) and the convincing immunoreactivity for p53 and Bcl-2 are also worrisome features. Note, however, that the protracted 16-year clinical course, absence of significant nuclear atypia, low mitotic activity (2 mitoses/50 hpf), and lack of clinical evidence of recurrence 1 year after surgery in this same case may be indicative of behavior of a more benign lesion.

Although normal glomus bodies have a microanatomical association with small, unmyelinated nerve fibers, an association with grossly evident nerve has been rarely described. In fact, to our knowledge, only 6 cases have been reported. Their clinicopathological features are summarized in Table 1. The tumors have affected the right common peroneal nerve, the radial nerve in the axillary region, the right sciatic nerve, a digital nerve, a dermal nerve in the shoulder, and the sural nerve (an incidental microscopic finding during a biopsy procedure for the evaluation of a distal symmetric sensorimotor neuropathy). All lesions occurred in adults, and 5 involved grossly apparent nerves. In the dermal example, the nerve association was a microscopic feature. The 6 tumors reported to date have ranged from < 1 mm to 5 cm in size, and thus, the large dimensions of the lesion in Case 1 make it exceptional. All le-

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**Fig. 5. Case 2.** A: Axial T2-weighted fast spin echo MR image with fat suppression showing focal enlargement of the distal median nerve in the arm (arrow) with hyperintense fascicles (arrowhead) immediately adjacent to the vascular portion of the lesion. B: Axial T1-weighted fast spoiled gradient image with fat suppression demonstrating enhancement of the dilated vascular portion of the tumor (arrow) as well as the neighboring individual nerve fascicles with interposing fat (arrowhead). C: Intraoperative photograph showing a purplish fusiform enlargement (arrow) of the median nerve affecting a fascicular group. This area was distinct from the remaining portion of the median nerve (arrowhead). D: Intraoperative photograph showing lesion dissection (arrow) away from the remaining median nerve, which appeared normal (arrowhead).
sions were discrete. The tumor described by Smith et al. as well as the lesion in Case 1 resembled benign peripheral nerve sheath tumors, specifically a schwannoma. Although the relatively large, discrete lesion described by Smith and colleagues “shelled out” with preservation of adjacent nerve fascicles, the tumors described in the present paper microanatomically infiltrated nerve fascicle and displaced the remainder of the sciatic (Case 1) and median (Case 2) nerves.

Additional cases of note include the following: 1) a small glomus tumor intimately associated with the volar branch of a digital nerve in a 39-year-old woman; 2) a vein-attached example compressing the lateral cutaneous nerve of the left forearm in a 64-year-old man; 3) a popliteal fossa glomangioma with extrinsic compression of the tibial nerve; 4) a glomus tumor arising near the posterior cutaneous branch of the ulnar nerve at the left wrist and mimicking a neuropathy in a 68-year-old man; 5) a 62-year-old man with right thigh pain and a 1.5-cm glomus tumor intimately bound to the obturator nerve; 6) extrinsic compression of the superficial peroneal nerve by a perioseal glomus tumor of the tibia; and 7) a unique example of a glomus tumor intimately associated with a traumatic neuroma in the right fourth finger of a 48-year-old man.

When a glomus tumor or glomangioma occurs in its typical dermis/subcutaneous location, it poses little difficulty in terms of a histological diagnosis, with the main entities of cutaneous adnexal tumors and intradermal nevi to be considered. The characteristic relationship of glomus cells to small vessels and its usual immunophenotype (SMA+, collagen IV+, S100−, and EMA−) are diagnostic features. However, when the tumor is encountered at an uncommon site, such as a nerve, other entities can be considered, including an epithelioid nerve sheath tumor, meningioma, epithelioid leiomyosarcoma, metastatic melanoma, or carcinoma. Again, the typical immunophenotype and the absence of cellular atypia and pleomorphism should suggest the right diagnosis.

Based on the literature as well as our experience with a massive glomus tumor and a glomangioma, it would ap-
### TABLE 1

**Literature summary of studies on glomus tumors involving peripheral nerve**

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Age (yrs), Sex</th>
<th>Symptoms/Signs</th>
<th>Nerve Involved</th>
<th>Lesion Size</th>
<th>Findings on Surgery</th>
<th>Findings on Pathological Analysis</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wing &amp; Leavitt, 1962</td>
<td>37, M</td>
<td>radiating pain in rt leg &amp; occasional tingling in lat 3 toes × 15 yrs; diffuse muscle atrophy throughout rt lower leg</td>
<td>rt common peroneal</td>
<td>1 cm</td>
<td>lesion shelled out w/ ease</td>
<td>gross: yellowish gray, partially encapsulated lesion; histological: glomus tumor, rare mitoses</td>
<td>NA</td>
</tr>
<tr>
<td>Kline et al., 1990</td>
<td>46, M</td>
<td>numbness &amp; tingling of thumb &amp; index finger; point tenderness at base of thumb; recent onset of cold insensitivity; + Phalen; + Tinel</td>
<td>ulnar digital nerve of lt thumb</td>
<td>“pea size”</td>
<td>glistening white mass arising w/in nerve fascicle; expanded epineurium; resected segment of fascicle</td>
<td>histological: glomus tumor; well circumscribed w/ pseudocapsule, peripheral myelinated fibers</td>
<td>complete resolution of pain; residual numbness along ulnar surface of thumb</td>
</tr>
<tr>
<td>Tropet et al., 1991</td>
<td>16, F</td>
<td>nonradiating rt pst thigh pain &amp; tenderness × 1 yr</td>
<td>rt sciatic</td>
<td>5 cm</td>
<td>oval, firm, yellowish, well-circumscribed tumor replacing nerve tissue; resection of nerve segment; external saphenous nerve graft placement</td>
<td>glomus tumor w/ fibrous capsule lacking mitoses w/ traversing nerve fibers; vimentin +; EM: cells w/ digitations, intracytoplasmic filaments, separated by “basaloid” material</td>
<td>partial recovery of motor function 2 yrs postop</td>
</tr>
<tr>
<td>Smith et al., 1992</td>
<td>62, F</td>
<td>paroxysmal pain arising in lt upper arm &amp; radiating to index &amp; middle fingers for 20 yrs; localized tenderness to palpation</td>
<td>lt radial</td>
<td>2.5 cm</td>
<td>well-encapsulated lesion shelled out w/ complete preservation of nerve fascicles</td>
<td>histological: glomus tumor w/ interspersed nerve twigs; PAS +, reticulin + intercellular material; MSA +; vimentin +</td>
<td>immediate resolution of pain w/out recurrent symptoms 1 yr postop</td>
</tr>
<tr>
<td>Calonje &amp; Fletcher, 1995</td>
<td>67, F</td>
<td>8 wk history of pain</td>
<td>dermal nerve in shoulder</td>
<td>1 cm</td>
<td>local excision</td>
<td>encapsulated, solid glomus tumor w/ intrafascicular growth; peripheral layer of perineurium; MSA +</td>
<td>no evidence of recurrence in 14 yrs</td>
</tr>
<tr>
<td>Donato et al., 2006</td>
<td>56, M</td>
<td>“distal symmetric sensorimotor neuropathy”</td>
<td>sural nerve</td>
<td>400 μm</td>
<td>sural nerve biopsy</td>
<td>well-circumscribed nodule in endoneurium: glomangioma; MSA +</td>
<td>NA</td>
</tr>
</tbody>
</table>

* EM = electron microscopy; MSA = muscle-specific actin; NA = not applicable; PAS = periodic acid–Schiff.
pear that a nerve-sparing surgical approach is recommended for treatment.

References
