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Perineurial cell tumor

Immunocytochemical and ultrastructural characterization. Relationship to other peripheral nerve tumors with a review of the literature

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Summary. A perineurial cell tumor occurred in the shoulder girdle of a 47 year old woman. Light microscopy demonstrated a well-differentiated spindle-cell neoplasm of uncertain histogenesis. Immunocytochemical staining for S-100 protein was negative. Ultrastructural study revealed tumor cells with characteristics of perineurium, e.g. large numbers of micropinocytotic vesicles, numerous intercellular junctions, and elongated cell processes surrounded by basal lamina. Tumors of perineurial cells should be distinguished from the commonly recognized schwannomas as well as from various soft tissue lesions so that their biologic behavior can be better defined. A review of three other reported cases of perineurial cell tumors suggested that these tumors are benign and are usually located in the extremities and shoulder girdle. In addition, perineurial cell proliferation has been identified in other lesions of peripheral nerves, such as neurofibromas and localized hypertrophic neuropathy. Immunocytochemical and ultrastructural study of spindle-cell lesions with unusual histologic features may reveal that perineurial cell proliferation occurs more frequently than currently recognized.

Key words: Peripheral nerve neoplasms – Peripheral nerve diseases – Nerve tissue protein S-100 – Perineurial cell

Introduction

Perineurial cell tumors are tumors composed of cells ultrastructurally similar to perineurial cells of peripheral nerves (Inaba et al. 1980; Kusama et al. 1981; Lazarus and Trombetta 1978). Since the recent recognition of this entity by Lazarus and Trombetta in 1978, two additional reports have appeared (Inaba et al. 1980; Kusama et al. 1981). The term "perineurioma"

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has been used in the recent literature for the entity also known as "localized hypertrophic neuropathy" (Bilbao et al. 1984; Mitsumoto et al. 1980), which contains perineurial cells as well as other cellular elements. Perineurial cells do not contain S-100 protein in contrast to Schwann cells which do contain this material (Stefansson et al. 1982; Weiss 1983).

We present an additional case of perineurial cell tumor and review the available literature. We draw a distinction between these lesions which contain an overwhelming predominance of perineurial cells and those lesions which include significant proportions of other cellular elements. We suspect that thorough immunocytochemical and ultrastructural study of unusual spindle-cell lesions may reveal that neoplasms and hyperplasias of perineurial cells occur more frequently than is currently recognized.

Clinical history

A 47-year old female was referred to Emory University Clinic for follow-up after removal of an asymptomatic mass from the right subclavicular area. The mass had been discovered on routine chest X-ray. A CT scan of the chest revealed a 2.5×2.5 cm well-circumscribed extrapleural mass that lay in the right shoulder girdle along the lateral margin of the trachea adjacent to the mid-portion of the right clavicle. Lymphadenopathy was not present. The mass was surgically excised and the margins appeared free of tumor. The light microscopic material was reviewed by pathologists at several institutions. Diagnoses ranged from low-grade fibrosarcoma to malignant schwannoma. Three months after the operation, CT scan showed no evidence of recurrent tumor. In the interim, electron microscopy had led to a diagnosis of perineurial cell tumor. No further procedures were performed.

The patient was in excellent health without evidence of recurrence or metastasis 31 months after surgery.

Materials and methods

The specimen was a circumscribed mass measuring 3 cm in diameter and weighing 12 g. The cut surface had a variably fibrous to fleshy appearance. Six hematoxylin and eosin stained sections made in other laboratories were available for review. Additional tissue was received in formalin solution and processed in our laboratory for light and electron microscopy. Histochemical stains including hematoxylin and eosin, Masson trichrome, Snook's reticulin, Alcian blue, Fontana-Masson, Grimelius and Bodian stains were performed on paraffin embedded material.

Immunoperoxidase cytochemistry for S-100 protein was performed on paraffin-embedded material. Control tissues included a benign schwannoma and a nerve with ganglion. Rabbit antiserum to bovine brain S-100 protein was obtained from Dako Corporation, Santa Barbara, CA, USA. Peroxidase-conjugated goat anti-rabbit IgG was obtained from Cappel Scientific Division of Cooper Biomedical, Malvern, PA, USA. A peroxidase substrate system consisting of 4-chloro-1-naphthol solution and hydrogen peroxide solution was obtained from Kirkegaard and Perry Laboratories, Inc., Gaithersburg, MD, USA. Normal rabbit serum was obtained in our laboratory.

Formalin-fixed tissue further processed for electron microscopy was diced into 1 mm cubes, post-fixed in 4% glutaraldehyde buffered with 0.1 M cacodylate, pH 7.4, and secondarily post-fixed in 1% osmium tetroxide buffered with Vernol-HCl, pH 7.4, prior to dehydration and embedding in epoxy. Semi-thin, one micron thick sections were stained with Paragon and appropriate areas were selected for ultramicrotomy. Ultrathin sections were stained with lead citrate and uranyl acetate and examined with a Philips 201 electron microscope.

Results

Light microscopy

A well-demarcated tumor was composed of spindle cells. Variable amounts of collagen were present in the stroma, giving some areas a hyalinized appearance. Other areas, containing little collagen, were highly cellular

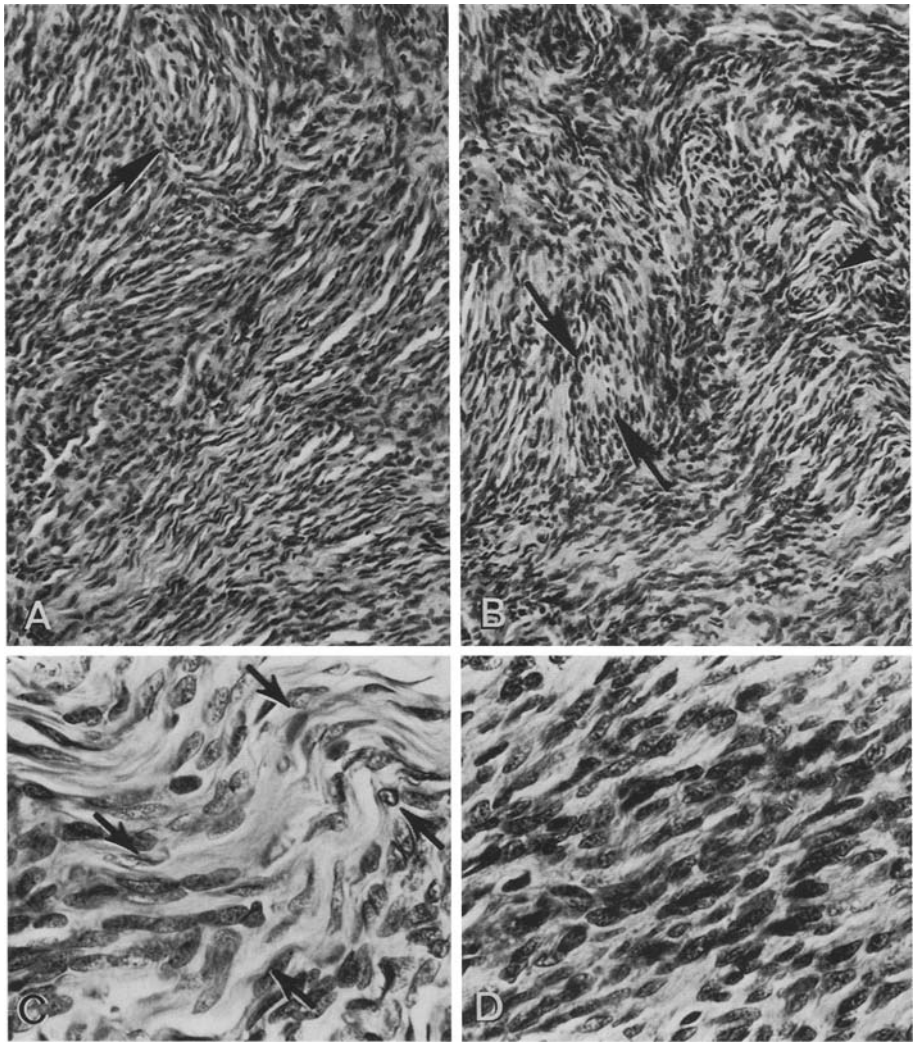

Fig. 1. A Most of the spindle-cell tumor is composed of fibrous, hyalinized areas (*upper right, lower right* and *lower left*). A whorl of cells is also present (*arrow*). Cell membranes are indistinct. Hematoxylin and eosin, ×115. **B** Occasional areas are composed of intersecting fascicles of spindle cells suggestive of a cartwheel ("storiform") pattern. A tactile-corpuscle-like structure (*arrowhead*) and a Verocay-like body (*arrows* on either side) are present. Hematoxylin and eosin, ×115. **C** Palisading of nuclei (*arrows* on either side) mimicking Verocay body formation. Hematoxylin and eosin, ×535. **D** Detail of moderately pleomorphic, vesicular nuclei found in the densely cellular areas of the tumor. Hemotoxylin and eosin, ×515

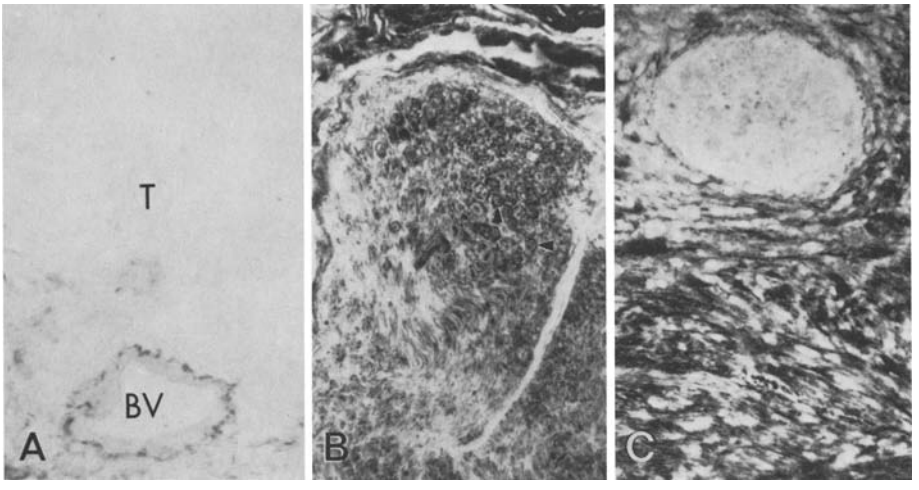

Fig. 2. **A** The perineurial cell tumor (*T*) does not stain with antibody to S-100 protein. A small blood vessel (*BV*) shows nonspecific staining. (Anti-S-100 immunoperoxidase, ×210). **B** The Schwann cells of the myelin sheath are positive (*arrowheads*) but the endoneurium is negative. Interestingly, axonal staining is variable. (Anti-S-100 immunoperoxidase, ×160). **C** A benign schwannoma is strongly positive with antibody to S-100 protein. (Anti-S-100 immunoperoxidase, ×185)

(Fig. 1A–D). Cells were arranged in nests and fascicles. Focal tendencies for a cartwheel ("storiform") pattern (Fig. 1B) and nuclear palisading were noted (Fig. 1B, C). The rounded nuclei varied moderately in size and shape, and indistinct nucleoli were rarely present (Fig. 1D). A few vacuolated nuclei were noted. Occasional mitotic figures could be identified. A few small aggregates of mononuclear inflammatory cells were seen. Several fascicles of peripheral nerve were present in the fibrous tissue surrounding the tumor, but Bodian stain failed to reveal nerve fibers within the tumor. Reticulin was variably present. Alcian Blue, Fontana-Masson and Grimelius stains were negative.

Immunocytochemistry

Tumor cells did not stain for S-100 protein (Fig. 2A). The adventitia of small blood vessels in the tumor and the adjacent fibrotic areas were weakly positive, and such areas were also positive in the positive control material, i.e. a benign schwannoma and a peripheral nerve with ganglion (Fig. 2B, C).

Electron microscopy

Spindle-shaped tumor cells formed elongated bipolar cell processes in a variably collagenous stroma (Fig. 3A). Basal lamina surrounded the cells, except in areas where cell membranes were closely opposed. In these latter areas, intercellular junctions were present (Fig. 3B). In addition, subplasmalemmal electron-dense condensations were frequently seen. Numerous smooth-surfaced micropinocytotic vesicles were observed along the plasma

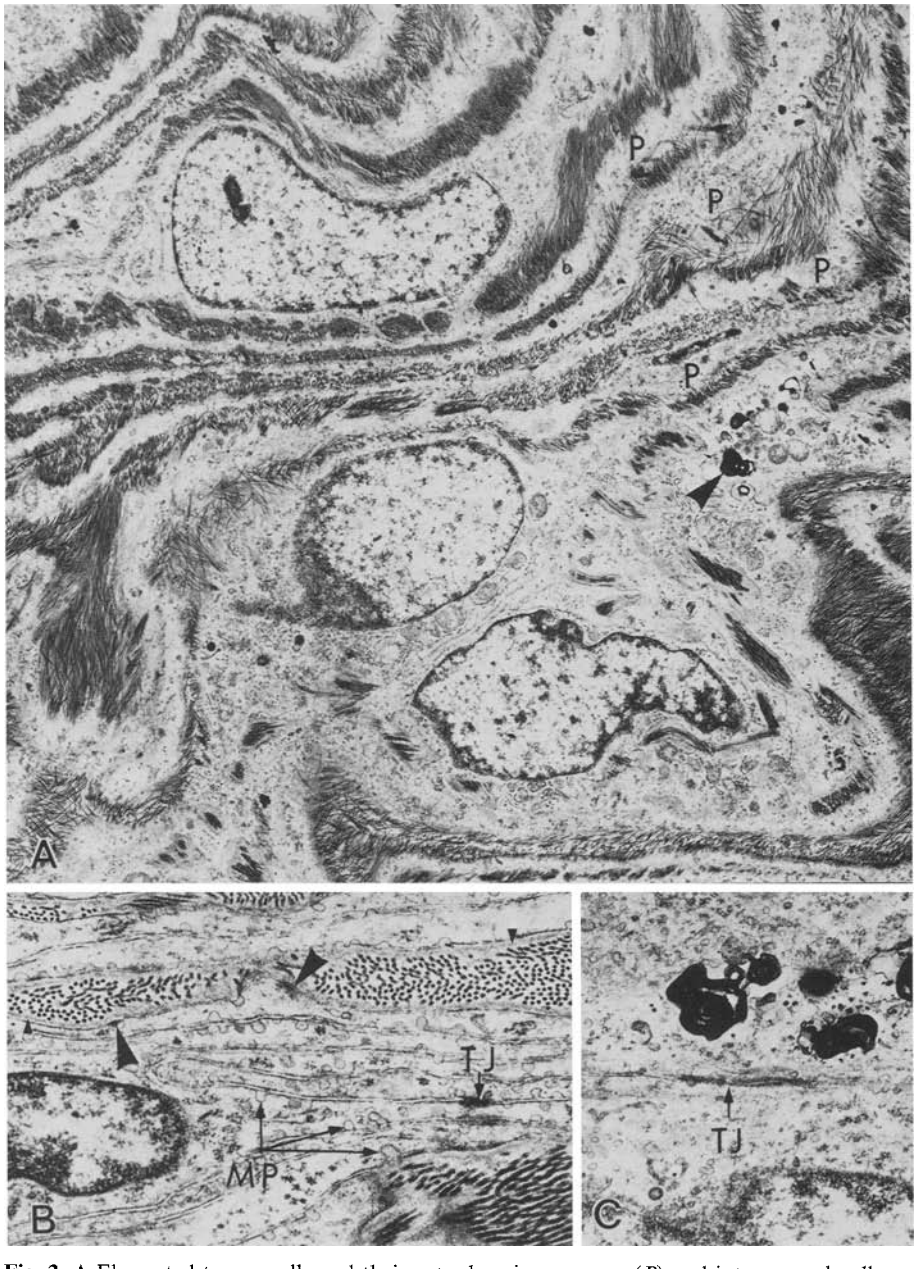

Fig. 3. A Elongated tumor cells and their cytoplasmic processes (*P*) and interspersed collagen. Occasional residual bodies (*arrowhead*) are present, ×3,900. **B** Parallel tumor cell processes with numerous smooth-surfaced micropinocytotic vesicles (*MP*) and prominent intercellular junction (*TJ*). Subplasmalemmal dense condensations (*large arrowheads*) and basal lamina (*small arrowheads*) are also present, ×5,150. **C** Residual bodies having structural features of myelin-like figures are seen adjacent to well-developed intercellular junctions (*TJ*), ×14,300

membranes (Fig. 3B). The cytoplasm contained small amounts of rough endoplasmic reticulum, scattered polyribosomes, few mitochondria and rare intermediate-type filaments. Occasional residual bodies were identified (Fig. 3C). Nuclear envelopes were oval with some irregularities. Finely-dispersed chromatin was present centrally and there was peripheral chromatin clumping. Small nucleoli were seen. No axons, Schwann cells or fibroblasts could be identified.

Discussion

The cells of this tumor have ultrastructural features similar to those of normal perineurial cells (Burkel 1967; Cravioto 1966; Ham 1974; Peters et al. 1976; Shantha and Bourne 1968; Thomas 1963). They are characterized by elongated cytoplasmic processes connected by frequent intercellular junctions. Basal (external) lamina is variably present, but it is particularly likely to be found at the periphery of cell groups. Numerous smooth-surfaced micropinocytotic vesicles are found on the plasma membranes (Inaba et al. 1980; Kusama et al. 1981; Lazarus and Trombetta 1978). Perineurial cells can be distinguished from Schwann cells because Schwann cells form interdigitating cytoplasmic processes bordered by a continuous basal lamina and because Schwann cells are connected by relatively few inconspicuous intercellular junctions and display only rare micropinocytotic vesicles. Fibroblasts differ from perineurial cells by the absence of basal lamina, the absence of intercellular junctions, and the presence of well-developed, often dilated cisternae of rough endoplasmic reticulum (Ghadially 1980).

Absence of staining for S-100 protein provides additional evidence for the perineurial cell origin of this tumor. Several other investigators have shown that perineurial cells are negative for immunoreactive S-100 protein whereas Schwann cells are positive with antibody directed against S-100 protein (Stefansson et al. 1982; Weiss 1983).

Although the immunocytochemical and ultrastructural features of perineurial cells are well-defined, the light microscopic appearance of perineurial cell lesions may cause diagnostic problems. For example, the present case was a densely cellular, spindle-cell lesion showing only focally features suggestive of its nerve sheath origin. Various soft tissue tumors were considered in the differential diagnosis. Immunocytochemical and ultrastructural study of unusual spindle-cell tumors should provide further information about the incidence of perineurial cell tumors. Their biologic behavior can then be better established.

We are aware of only three other well-documented cases of localized neoplasms predominantly composed of perineurial cells verified by ultrastructural study (Table 1). None of these was studied by anti-S-100 protein immunocytochemistry. A fourth case is illustrated in an atlas of electron microscopy, but no historical details are available for it (Henderson and Papadimitriou 1982) and it is therefore omitted from Table 1. Identification of such tumors has been possible only since electron microscopy became widely available for diagnostic purposes. The three previously well-docu-

Table 1. Reported cases of ultrastructurally confirmed tumors consisting only of perineurial cells[a]

Case No	Age	Sex	Site	Attached to nerve?	Light microscopic diagnosis	Follow-up	Date (Ref)
1	45	M	Calf	No	Neurofibroma	Not given	Lazarus and Trombetta (1978)
2	51	F	Forearm	No	Neurofibroma	Not given	Inaba et al. (1980)
3	31	F	Mandible	"Related to" nerve	Perineurioma variant of neurilemmoma	1 year	Kusama et al. (1981)
4	47	F	Shoulder girdle	?		31 months	Present case

[a] Axons, Schwann cells and fibroblasts were not described in these cases. The case included in the ultrastructural atlas of Henderson and Papadimitriou is not included because of a lack of pertinent clinical information

mented cases presented as mass lesions, as did our case. Three of these four cases occurred in the extremities or shoulder girdle, and the fourth case occurred in the mandible. Interestingly, only the tumor from the mandible was described as "related to" a nerve. The mean age of the four patients at presentation was 43.5 years. One male and three females were afflicted. Although little follow-up information is available, no instance of recurrence or metastasis has been documented.

Perineurial cells have been found in other peripheral nerve sheath tumors. For example, these cells have been identified in neurofibromas. Most recently, Erlandson and Woodruff (1982) concluded that perineurial cells were the principal constituents of ten neurofibromas examined. Other workers applied the same morphologic criteria (Erlandson and Woodruff 1982), i.e. those used in the present study, to identify perineurial cells, Schwann cells and fibroblasts. Twelve neurofibromas were examined by electron microscopy and differential cell counts were performed (Lassman et al. 1977). Small proportions of perineurial cells (0.7%–8.6%) intermingled with Schwann cells and fibroblasts were found in 11 of 12 tumors. The twelfth case contained 31% perineurial cells. These same workers, after finding a disorganized network of perineurial cell processes at the junction between nerve fascicles and neurofibromas, also suggested that perineurial cells take part in neurofibroma formation (Lassman et al. 1976). Other investigators found perineurial cells in the tactile-like structures of neurofibromas and also concluded that these cells take part in oncogenesis (Smith and Bhawan 1980; Weiser 1975). S-100 immunocytochemistry provides further support for the presence of perineurial cells in neurofibromas. All of the neoplastic cells are not positive; these negative cells could represent perineurial cells (Weiss et al. 1983). Differences in the proportions of perineurial

and other cells found in neurofibromas might explain the variations in histologic pattern demonstrated by these tumors (Weller and Cervos-Navarro 1977). Further investigation may be necessary before the nature of the cellular constituents of neurofibromas is clarified.

Large numbers of perineurial cells have also been found in the diffuse enlargement of long segments of a single peripheral nerve, an entity known variously as "localized hypertrophic neuropathy" (Mitsumoto et al. 1980), "intraneural neurofibroma" (Lallemand and Weller 1973), "hypertrophic mononeuropathy" (Hawkes et al. 1974; Peckham et al. 1982), and recently "perineurioma" by some authors (Bilbao et al. 1984; Mitsumoto et al. 1980). This condition is distinguished from the generalized hypertrophic neuropathies, where Schwann cell proliferation produces the onion bulb formations (Asbury and Johnson 1978), by ultrastructural identification of the cell type as well as by clinical involvement of only one nerve. Axons and Schwann cells are also present in these lesions. While several authors consider this nerve enlargement neoplastic (Bilbao et al. 1984; Mitsumoto et al. 1980), others have suggested that these lesions could be caused by trauma, especially since they are common in the posterior interosseous nerve (Asbury and Johnson 1978; Hawkes et al. 1974; Ochoa and Neary 1975; Weller and Cervos-Navarro 1977). Indeed, although Lallemand and Weller originally believed their two cases to be neoplastic, Weller (1974) later reconsidered the possibility of trauma as an etiologic factor. Hawkes and coworkers (1974) speculated that their lesion was caused by recurrent segmental demyelination possibly related to trauma. Although they described "Schwann cells" in their lesion, review of their description and illustrations suggests that some of these cells may be perineurial cells. It, therefore, appears that proliferations of perineurial cells may form well-defined masses composed of a single cell type, or may participate in the segmental enlargement of a nerve. However, the term "perineurioma" might better be reserved for discrete masses almost entirely composed of perineurial cells without evidence of residual axons or Schwann cells.

In summary, we have documented a fifth case of a perineurial cell tumor arising in the shoulder girdle of a 47 year old woman. Immunocytochemical and ultrastructural study is necessary for definitive diagnosis of these spindle-cell lesions. Perineuriomas represent one end of a spectrum of proliferation of this cell type and we agree with others (Henderson and Papadimitriou 1982; Inaba et al. 1980; Lazarus and Trombetta 1978) who believe that such tumors represent a third category of peripheral nerve tumor, immunocytochemically and ultrastructurally distinct from the more readily recognized schwannomas and neurofibromas.

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