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Neurogenic sarcomas in patients with neurofibromatosis (von Recklinghausen's disease)

Light, electron microscopy and immunohistochemistry study

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Summary. Thirteen soft tissue neurogenic sarcomas from twelve patients with neurofibromatosis (Von Recklinghausen's disease) were ultrastructurally examined. Electron microscopic studies revealed a wide spectrum of morphological manifestations varying from schwannian to fibroblastic, histiocytic, fibrohistiocytic and relatively undifferentiated cellular proliferations. A similar variation on light microscopic appearances has been previously reported in these neurogenic sarcomas. Neurogenic sarcomas occurring in patients with neurofibromatosis (Von Recklinghausen's disease), represent a heterogenous group of neoplasms with various patterns of differentiation identified ultrastructurally. The morphologic expressions of these neurogenic neoplasms can be conceptualized as a disorderly growth of the various peripheral nerve cellular components, or, as has been previously suggested, as a result of the multipotential nature and metaplastic ability of Schwann cells. S-100 protein immunohistochemistry was only positive in those neoplasms ultrastructurally proven to represent schwannian cellular proliferations.

This study serves to document the range of fine structure that may be found in neurogenic sarcomas, to correlate the ultrastructural findings with the light microscopic appearance of these tumors, to determine the specificity of the electron microscopic findings, and immunohistochemistry for S-100 protein and assess their possible value in differential diagnosis.

Key words: Neurofibrosarcomas – Neurogenic sarcomas – Von Recklinghausen's disease – Malignant schwannomas – Ultrastructure

Quick and Cutler (1927) and Stewart and Copeland (1931) described neurogenic sarcomas. The term neurogenic sarcoma denotes malignant neo-

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plasms which despite diverse morphology, all originate in peripheral nerves. Histologic features useful in suggesting a neural derivation for these neoplasms include geographic necrosis, aligned spindle cells with nuclear palisading, cellular arrangement around blood vessels in a whorled pattern, and admixed cellular and myxoid areas.

In general, the light microscopic appearance of neurogenic sarcomas is quite variable and specific findings such as the ones mentioned are sometimes only focally present and may even be absent in some cases (Harkin and Reed 1969). As a result, a diagnosis of neurogenic sarcoma might be difficult or even impossible at the light microscopic level. Recently, S-100 protein immunohistochemistry has been suggested to play a promising role in the diagnosis of these cases (Weiss et al. 1983). Some authors have suggested that neurogenic sarcomas represent a homogeneous group of malignant schwannomas (Guccion and Enzinger 1979; Ghosh et al. 1973; Mackay et al. 1975). Taxy et al. (1981) have attempted at defining ultrastructural criteria for diagnosis of neurogenic sarcomas and in examining five such cases noted some variability in their electron microscopic appearances; however, the authors still classified all the neoplasms as malignant schwannomas. Trojanowski et al. (1980) have addressed the problems that are encountered when attempting accurate diagnoses of malignant nerve sheath neoplasms. They emphasized the difficulties that exist in determining the origins of these neoplasms from peripheral nerves and in predicting prognosis.

Electron microscopic studies of neurogenic sarcomas have been conducted (Markel and Enzinger 1982), but the entire spectrum of ultrastructural appearances has not been fully explored. Patients with neurofibromatosis (Von Recklinghausen's disease) represent an appropriate group to study the ultrastructure of these tumors due to their propensity to develop neurogenic sarcomas. Guccion and Enzinger (1979) studied 46 soft tissue neoplasms associated with Von Recklinghausen's neurofibromatosis which they considered to represent malignant schwannomas on the basis of light microscopic examination alone. They recognized variable histological appearances in these tumors. Erlandson and Woodruff (1982) studied ten malignant peripheral nerve sheath tumors and concluded that malignant tumors derived from nerve sheaths are in general poorly differentiated sharing features with Schwann and perineural cells. Cell forms intermediate between these cells and fibroblasts were noted in these cases. The present authors studied thirteen malignant peripheral nerve neoplasms arising in patients with neurofibromatosis with the purpose of correlating light, electron microscopic, and S-100 protein immunohistochemistry findings.

Materials and methods

Thirteen specimens from soft tissue tumors occurring in patients with neurofibromatosis (Von Recklinghausen's disease) considered to represent neurogenic sarcomas were studied by both light and electron microscopy. There was documented clinical evidence of neurofibromatosis with multiple neurofibromas and "cafe au lait" spots, as well as family history, identified in all cases. Table 1 summarized pertinent clinical data and location of the neoplasms studied.

The accessions included twelve primary and one metastatic soft tissue tumors. Two specimens were obtained from one patient, a primary soft tissue sarcoma and an additional neoplasm interpreted as metastatic (Cases 2 and 3, Table 1).

Tissue obtained for light microscopy was fixed in formalin and sections were stained with hematoxylin and eosin and trichrome stains, as well as Alcian blue stain in the myxoid variants.

One mm cubes of tissue from representative portions of the neoplasms were fixed for electron microscopy in 2% buffered glutaraldehyde and embedded in Epon. Three of the cases were obtained from formalin – fixed tissues subjected to immersion through a series of ethanol solutions with decreasing concentration and subsequent glutaraldehyde fixation. Thick sections were stained with toluidine blue. Thin sections were stained with lead citrate and uranyl acetate. At least two different sections were examined using a Hitachi HU-11-C transmission electron microscope. All tumors were confirmed to be originating from peripheral nerves by dissection or origin from previously diagnosed neurofibromas. All tumors fulfilled malignant criteria by light microscopy including high mitotic index, necrosis, invasiveness, and/or distant metastases.

A representative section from each case was stained for the presence of S-100 protein using corresponding antisera and following the usual immunohistochemical methods. Immunohistochemistry staining was performed after the light and electron microscopic analysis had been performed and interpreted.

Light microscopy

At least six different light microscopic patterns were recognized. Some of the cases showed spindle cells with a tendency toward nuclear palisading, geographic necrosis, and occasional eosinophilic acellular areas disposed in between rows of regularly aligned cells mimicking Verocay bodies (Figs. 1, 2A). This schwannian pattern was sometimes the only identifiable pattern and in other cases was a focal finding. Two of the cases showed elongated cells with pointed nuclei and wavy cytoplasm. In one case, the cells disposed themselves displaying a herringbone pattern such as that classically described in fibrosarcomas (Fig. 2B). Interlacing bundles of spindle cells with blunted nuclei but lacking identifiable intracytoplasmic myofilaments were present in one case; this pattern was reminiscent of a leiomyosarcoma (Fig. 3). In two cases, one focally and in the other representing the predominant pattern, numerous bizzare multinucleated giant cells were seen admixed with spindle cells. Both cellular components were arranged displaying a storiform pattern typical of malignant fibrous histiocytoma (Fig. 4). A fifth pattern lacked a recognizable cellular arrangement and was mainly composed of small, rather undifferentiated round to ovoid cells (Fig. 5A). A myxoid cellular pattern was also noted in focal areas of an otherwise typical schwannian neoplasm, and in one case, as the predominant pattern of cellular arrangement (both neoplasms in the same patient) (Fig. 5B). Table 1 details the patterns identified in the respective cases.

Immunohistochemical staining for S-100 protein was strongly and diffusely positive in 8 of 13 cases. Four cases were entirely negative and one case was focally positive. Table 1 clarifies this data.

Electron microscopy

Several different patterns were noted on electron microscopic examination. The majority of the cases (eight) showed elongated cells with interdigitating cell processes (Figs. 6 and 7). One neoplasm showed this same finding in a focal area. In the areas of interdigitation, well defined intercellular junctions were seen (Figs. 7B, 8C, circle). In the cellular processes, collections of microtubules were often identified (Fig. 7B). Surrounding the cell membranes a sometimes fragmented basal lamina was noted in nine cases (70% of all neurogenic sarcomas) (Figs. 8A, 7B, b1). Evidence of pinocytotic activity at the cell surfaces was an additional finding (Figs. 8B, arrows and 8A, C, arrows). Occasionally, large multinucleated cells were present with similar ultrastructural characteristics as the previously mentioned mononuclear

Table 1. Neurogenic sarcomas – clinical data, correlation of light and electron microscopic findings, relationship to peripheral nerves and results of S-100 protein immunohistochemistry – general light microscopic pattern: neoplastic growth of spindle cells creating a sarcomatous growth pattern

Case	Age	Sex	Location	Light microscopy special features	Electron microscopy	Immuno-histo-chemistry S-100 pattern	Arising from peripheral nerve as determined by dissection of specimen
1	11	M	Left chest wall	Non-geographic and geographic necrosis, focal storiform pattern, no giant cells	Histiocytic cellular proliferation	–	Yes
2[a]	51	M	T_3–T_5 spinal column	Solid growth, focal pallisading, geographic necrosis, myxoid areas	Schwannian cellular proliferation	+, diffuse	Yes
3[a]	51	M	Left chest wall	Solid growth, focal pallisading, geographic necrosis, predominant pattern with myxoid areas	Schwannian cellular proliferation	+, diffuse	No
4	36	M	Left thigh	Questionable areas with pallisading, empty eosinophilic areas between rows of cells resembling Verocay bodies	Fibroblastic and histiocytic proliferation	–	Yes
5	23	M	Left forearm & axilla	Storiform pattern, numerous multinucleated giant cells – MFH pattern	Schwannian cellular proliferation	+, diffuse	Yes
6	23	F	Right axilla	Interlacing bands of cells with blunted nuclei and eosinophilic cytoplasm. Leiomyosarcomatous pattern	Schwannian cellular proliferation	+, diffuse	No

7	50	F	Right arm	Geographic necrosis, pallisading Verocay bodies	Schwannian cellular proliferation	+, diffuse	Yes, radial nerve
8	38	M	Left temple	Solid growth with herringbone pattern, fibrosarcomatous appearance, focal geographic necrosis	Fibroblastic cellular proliferation	–	No
9	33	F	Right neck	Geographic necrosis, pallisading, focal herringbone pattern, cells showing fibrillary, wavy cytoplasm	Schwannian cellular proliferation	+, diffuse	Yes, spinal accessory nerve
10	54	M	Right hip	Interlacing bands of cells with blunted nuclei and eosinophilic cytoplasm, focal necrosis, leiomyosarcomatous pattern	Predominant schwannian cellular proliferation with focal fibrous/histiocytic proliferation in one area	+, diffuse	No
11	50	F	Scalp	Solid cellular growth, no specific recognizable pattern	Undifferentiated cellular proliferation with focal schwannian differentiation	+, focal	No
12	41	M	Right neck	Solid growth with swirling cellular proliferation	Schwannian cellular proliferation	+, diffuse	No
13	35	F	Left sacrum	Storiform pattern, multinucleated giant cells, focal necrosis – MFH pattern	Fibroblastic & histiocytic cellular proliferation	–	No

[a] 2 and 3 represent neurogenic sarcomas from the same patient

MFH – Malignant fibrous histiocytoma pattern

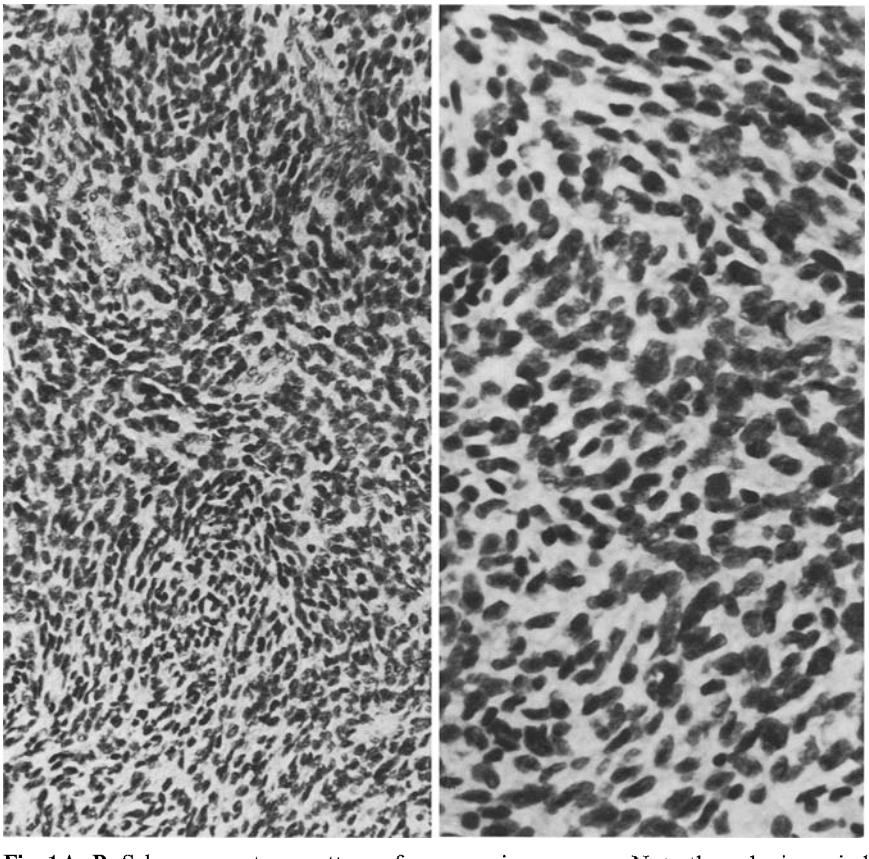

Fig. 1A, B. Schwannomatous pattern of neurogenic sarcomas. Note the cohesive spindle cell pattern associated with small blood vessels. Magn. **A** ×350, **B** ×700

cellular components. Extracellular long-spacing collagen was identified in two cases (Fig. 7C) (16% of all neurogenic sarcomas). This ultrastructural pattern is that associated with neoplasms derived from Schwann cells. One neoplasm was composed of a homogeneous proliferation of spindle fibroblastic cells with prominent nucleoli and abundant cytoplasm containing dilated cisternae of rough endoplasmic reticulum. Collagen fibers were identified closely adherent to the cell membranes. In an additional tumor, the cells were noted to be rather small with ovoid nuclei and devoid of significant differentiation. Scattered cellular organelles were noted in the cytoplasmic matrix. Small cellular processes without microtubular aggregates were only focally seen. Significant interdigitation and intercellular junctions joining apposing cellular membranes were absent. Basal lamina material covering the cell membranes and pinocytotic activity were not prominent in this cellular pattern. In an additional case, in addition to fibroblastic cellular components, there were large cells with abundant cytoplasm containing lipid globules (outlined arrows), as well as numerous lysosomal bodies (dark arrows) (Fig. 9A, B). The cells showed thin pseudopodia extending from the main cell bodies and no evidence of significant cohesion. An additional ultrastructural type of these neoplasms revealed a monotonous proliferation of the above mentioned large cells with abundant cytoplasm and numerous cytoplasmic organelles widely dispersed throughout the cytoplasmic matrix (Fig. 9C, D). No fibroblastic cells were identified in this last ultrastructural pattern. In one case two types

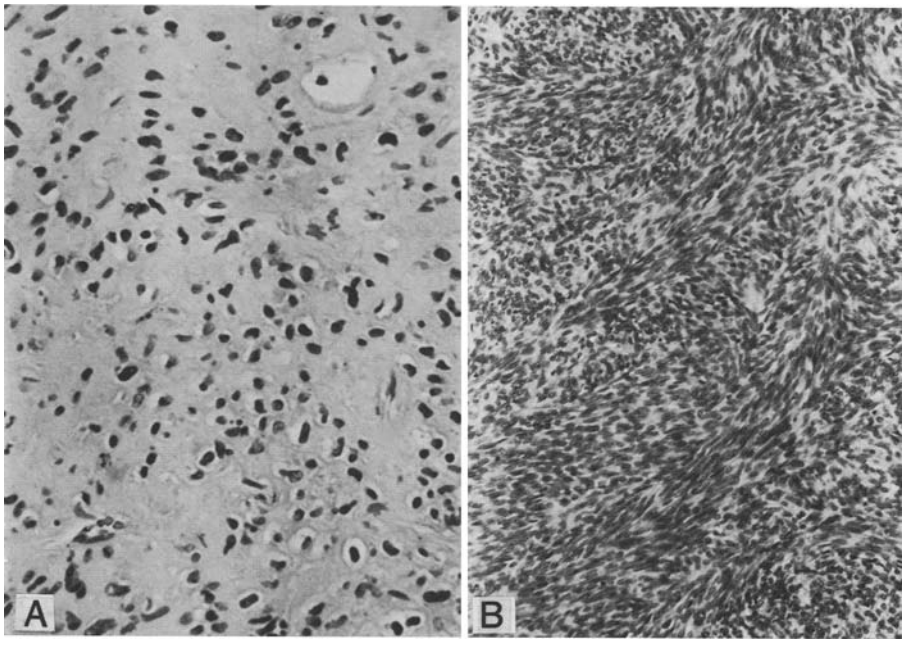

Fig. 2A, B. Additional schwannian pattern of differentiation with well defined eosinophilic acellular areas in between rows of proliferating cells. Note attempt at pallisading in focal areas, as well as acellular areas in between rows of neoplastic cells. In **B** note fibrosarcoma pattern of neurogenic sarcoma. Note herringbone pattern. Magn. **A** ×160, **B** ×350

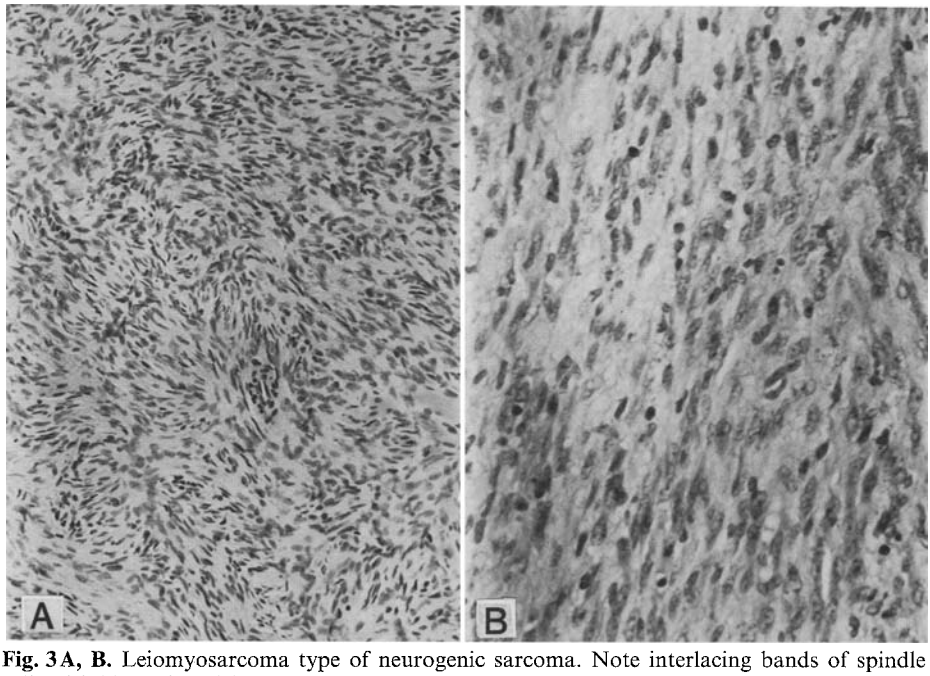

Fig. 3A, B. Leiomyosarcoma type of neurogenic sarcoma. Note interlacing bands of spindle cells with blunted nuclei. Magn. **A** ×350, **B** ×700

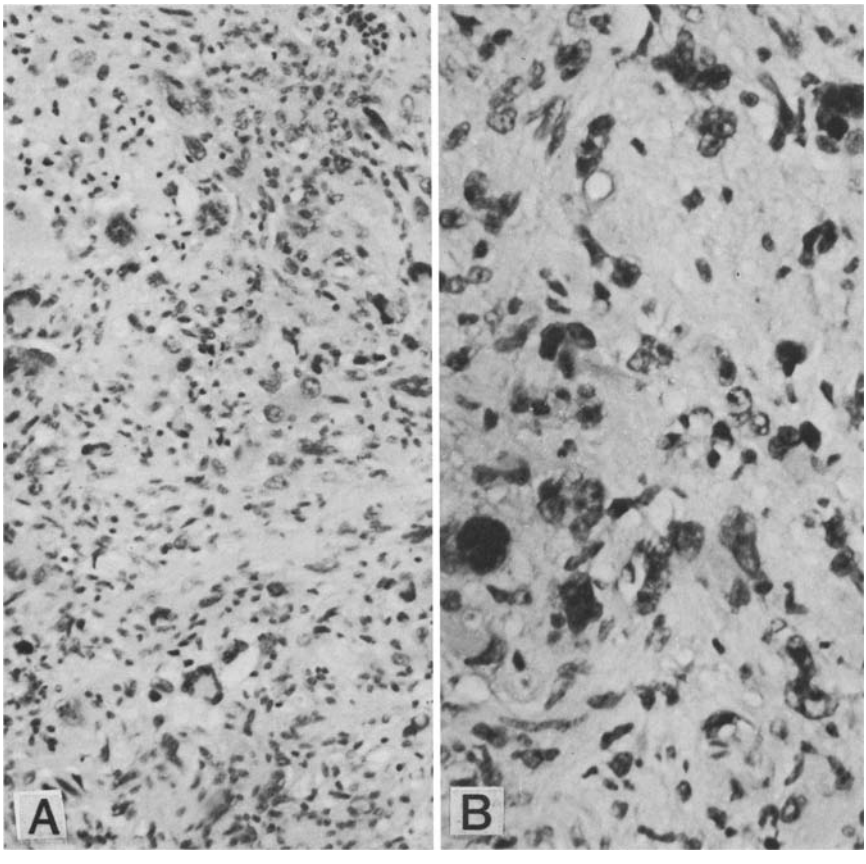

Fig. 4A, B. Note the overall storiform pattern to the lesion. Numerous multinucleated giant cells, some bizarre, typical of this fibrous histiocytoma-like pattern of neurogenic sarcoma are illustrated. Magn. **A** ×350, **B** ×700

of cellular proliferation were identified in different areas of the tumor. A predominant schwannian pattern was seen and in a focal area a fibrous histiocytoma appearance was observed. In none of the cases, was there ultrastructural evidence of smooth or skeletal muscle differentiation. Table 1 details the different ultrastructural patterns as related to light microscopic appearances of specific cases.

Discussion

Neurogenic sarcomas are denominated as such provided that at least some of the microscopic schwannian patterns can be recognized or by gross dissection establishing their origin from a peripheral nerve. A history of Von Recklinghausen's disease, a disease which has as its central feature a disorderly growth of peripheral nerve components, is further suggestion of the neurogenic origin of these neoplasms.

Gore (1952) described a variety of unusual light microscopic patterns in neurogenic sarcomas. Neurogenic sarcomas may assume the microscopic

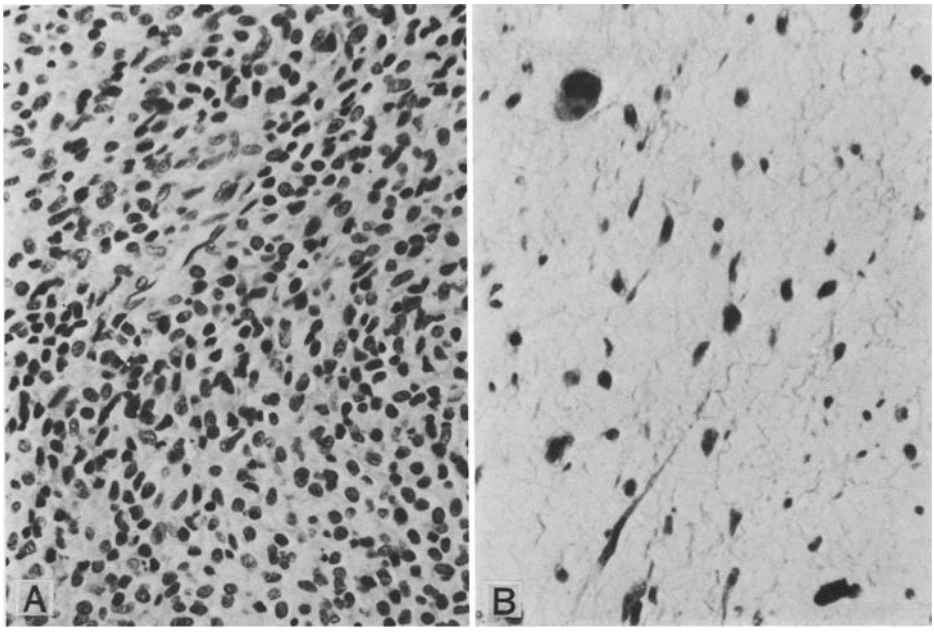

Fig. 5A. Note overall undifferentiated pattern of this neurogenic sarcoma in **A**. The proliferating cells are rather small, round and not arranged in any specific pattern. In **B** note myxoid pattern of neurogenic sarcoma. Note the myxoid background stroma. The predominating cells are spindle cells with wavy cytoplasm and these are intermixed with scattered large multinucleated cells. Magn. **A** ×350, **B** ×700

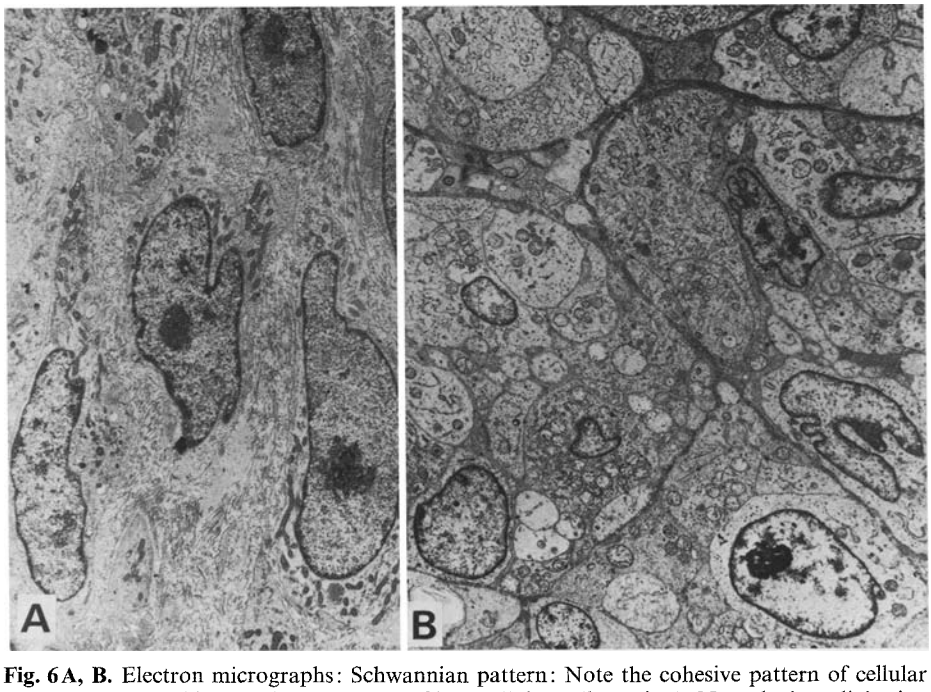

Fig. 6A, B. Electron micrographs: Schwannian pattern: Note the cohesive pattern of cellular arrangement noted in **B** and the presence of intercellular collagen in **A**. Note the interdigitating cellular processes forming a jigsaw puzzle-type of arrangement in **B**. Magn. **A** ×6,500, **B** ×2,600

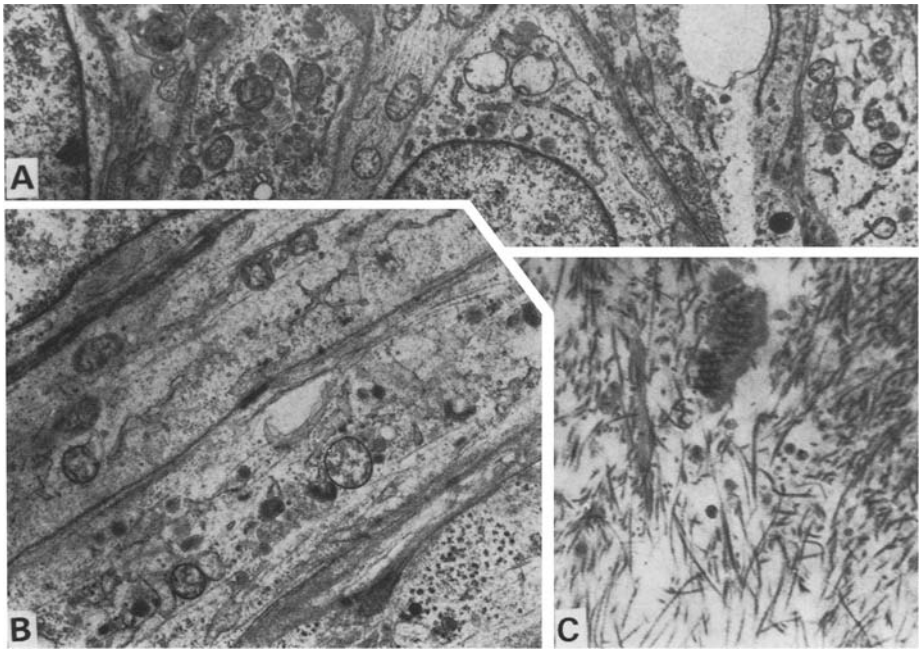

Fig. 7A–C. Electron micrographs: Schwannian pattern: Note in **A** the interdigitation of adjacent cellular membranes. In **B** well defined junctions are seen joining apposing cellular membranes. Collections of microtubules are noted within the cellular processes. Note at the bottom of the photograph the presence of basal lamina material surrounding the cell membrane in an area where close cell opposition is not noted. In **C** note the long-spacing collagen identified in the intercellular stroma in some of these neurogenic sarcomas. Magn. **A** ×13,000, **B** ×22,000, and **C** ×17,500

appearance of rhabdomyosarcoma, fibrosarcoma, fibrous histiocytoma, leiomyosarcoma, or even liposarcoma. It has been suggested that perhaps it would be appropriate to list the elements recognized within a specific neurogenic sarcoma by light microscopy. This would provide a more detailed analysis of these neoplasms and perhaps histologic variations could be used later to correlate with tumor behavior and patient's prognosis. No electron microscopic studies have been conducted to prove or disprove the presence of such suspected cellular components. Light microscopy alone is probably not enough to characterize these tumors. Some light microscopic patterns suggestive of a type of cellular proliferation may prove to show ultrastructural features indicative of a different type of proliferating cell. One of the authors has recently observed that malignant soft tissue tumors with multinucleated giant cells and a storiform pattern suggestive of malignant fibrous histiocytomas on light microscopy, may prove to represent schwannian neoplasms when examined ultrastructurally (Herrera et al. 1982). S-100 protein has been recently considered to represent a marker for schwannian neoplasms (Weiss et al. 1983).

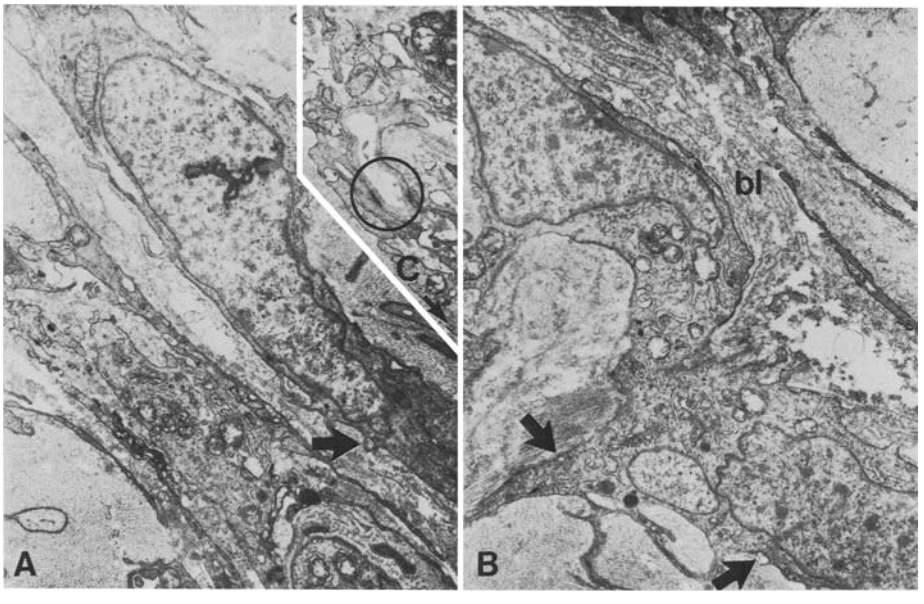

Fig. 8A–C. Note in (**A**) the elongated cells with well defined basal lamina material covering the cellular membranes (b1), and interdigitating cytoplasmic processes from adjacent cells. Note in (**B**) a binucleated cellular component with schwannian ultrastructural characteristics and prominent reduplicated basal lamina covering the cellular membranes. Note in (**C**, *insert*) interdigitating cellular processes joined by immature intercellular junctions (*see circle*) and evidence of pinocytotic activity at the cell membranes (*see arrows* in **A, B,** and **C**). Magn. **A** ×6,250, **B** ×6,250, and **C** ×6,250

If the pluripotential nature of Schwann cells is considered, it is not surprising that neurogenic sarcomas may mimic other spindle cell sarcomas such as various myxoid sarcomas, leiomyosarcoma, fibrosarcoma, monophasic synovial sarcomas, rhabdomyosarcomas, and even others in their light microscopic appearance. The question remains whether these tumors when examined ultrastructurally actually represent different cell types. This study demonstrates that most of the malignant soft tissue neoplasms arising in patients with Von Recklinghausen's disease actually represent malignant schwannomas regardless of their light microscopic appearance. However, some of the neurogenic sarcomas studied showed a monotonous proliferation of fibroblastic cells indistinguishable from fibrosarcomas ultrastructurally; others had a mixture of fibroblasts and histiocytic cells indicative of a fibrous histiocytoma, and in still others the cellular proliferation was exclusively composed of histiocytic cells. Two of the tumors on light microscopy resembled a leiomyosarcoma; however, when examined ultrastructurally showed schwannian derived features. The authors could not correlate light microscopic appearances using recognizable patterns of cellular arrangement directly with ultrastructural findings in most cases. Direct continuity with nerve trunks was noted in two of the four neoplasms which lacked

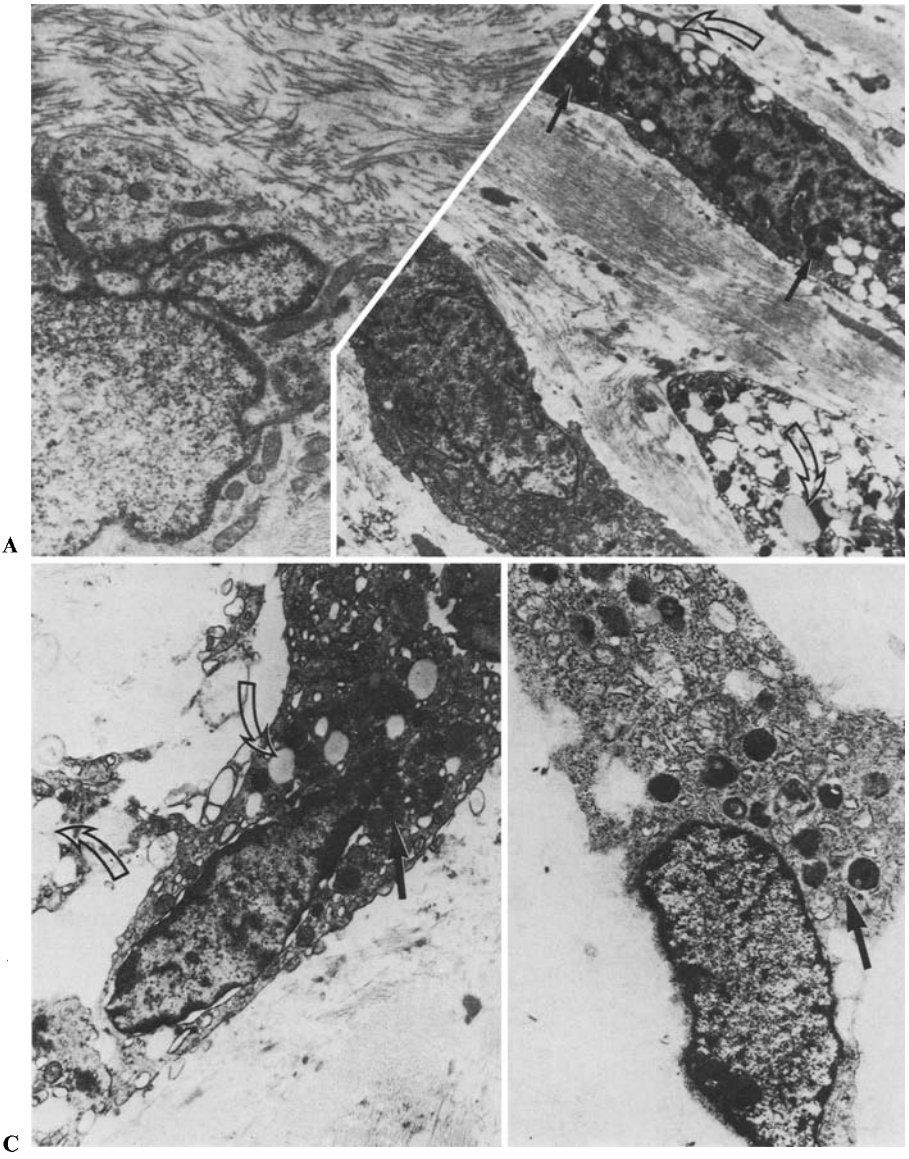

Fig. 9A–D. Electron micrographs: Fibrous histiocytoma-type of neurogenic sarcoma. Contrast **A** showing a cell with abundant rough endoplasmic reticulum in its cytoplasm associated with numerous collagen fibers and B where a mixture of fibroblastic cells (*left bottom*) and histiocytic cells (*right*) is noted. In **C** note histiocytoma-type of neurogenic sarcoma. Note in both **C** and **D** cells with histiocytic characteristics as evidenced by the presence of abundant cytoplasm containing numerous organelles and collections of lysosomal bodies and lipid globules (dark arrows – lysosomes, curved outlined arrows – lipid globules). Magn. **A** ×22,000, **B** ×16,500, **C** ×13,000, and **D** ×13,000

schwannian characteristics and in four of the eight with Schwann cell differentiation.

The immunohistochemical results using antibody to S-100 protein were indeed most interesting in that all eight cases that were diffusely positive showed typical schwannian ultrastructural characteristics. The neoplasm felt to be essentially undifferentiated but which showed some schwannian features was also focally positive for S-100 protein. On the other hand, the four cases found to be negative for S-100 protein when examined ultrastructurally showed fibroblastic, histiocytic and/or fibrohistiocytic characteristics. These results emphasize that the presence of S-100 protein positivity is not a constant finding in neurogenic sarcomas and that only schwannian neoplasms appear to be positive for S-100 protein.

Findings in this study indicate that a considerable range of fine structure may be observed in neurogenic sarcomas and that S-100 protein is not always positive in neurogenic sarcomas. It should be recognized that it is sometimes impossible to differentiate between a malignant fibrous histiocytoma or a fibrosarcoma and a neurogenic sarcoma, even at the ultrastructural level.

The question remains whether the morphologic expressions of these neurogenic sarcomas are a manifestation of the metaplastic ability of Schwann cells. Some authors consider Schwann cells as pluripotential cells which can multiply and proliferate like fibroblasts and assume phagocytic properties by converting into histiocytes (D'Agostino et al. 1963; Vieta and Pack 1951). The morphological manifestations that were noted in these tumors could be entirely explained on this basis.

A different explanation may be given for the heterogenicity of the cellular lines identified by electron microscopy. Neurogenic sarcomas may result from proliferation of the different cellular components of peripheral nerves. Reflecting on the normal structure of peripheral nerves, it is not difficult to understand how different cellular components could proliferate and give rise to the various morphologic manifestations of neurogenic sarcomas that were documented in this ultrastructural study (see Fig. 10). The variability of S-100 positivity in these cases is perhaps suggestive of this theory rather than the hypothesis of metaplastic schwannian cells. Skeletal muscle differentiation (as found in "Triton tumors"), or osseous and cartilaginous differentiation, as has been reported in some neurogenic sarcomas (Markel and Enzinger 1982; Quick and Cutler 1927), however, would require a metaplastic process, involving most likely Schwann or perineural cells.

A generally poor prognosis has been reported in neurogenic sarcomas originating in pre-existing neurofibromas in association with Von Recklinghausen's disease (Hajdu 1979; White 1971). A worse prognosis has been noted in these tumors when associated with neurofibromatosis than when found without the stigmata of Von Recklinghausen's disease (Hajdu 1979; D'Agostino et al. 1963). Neurilemmomas composed entirely of Schwann cells have been stated to rarely (almost never) undergo malignant transformation (Stout 1935; Stout 1946; Bertrand and Bernard 1930; Brandes 1933; Denecke 1932; Fittipaldi 1932; Guleke 1926; Carstens and Schrodt 1969),

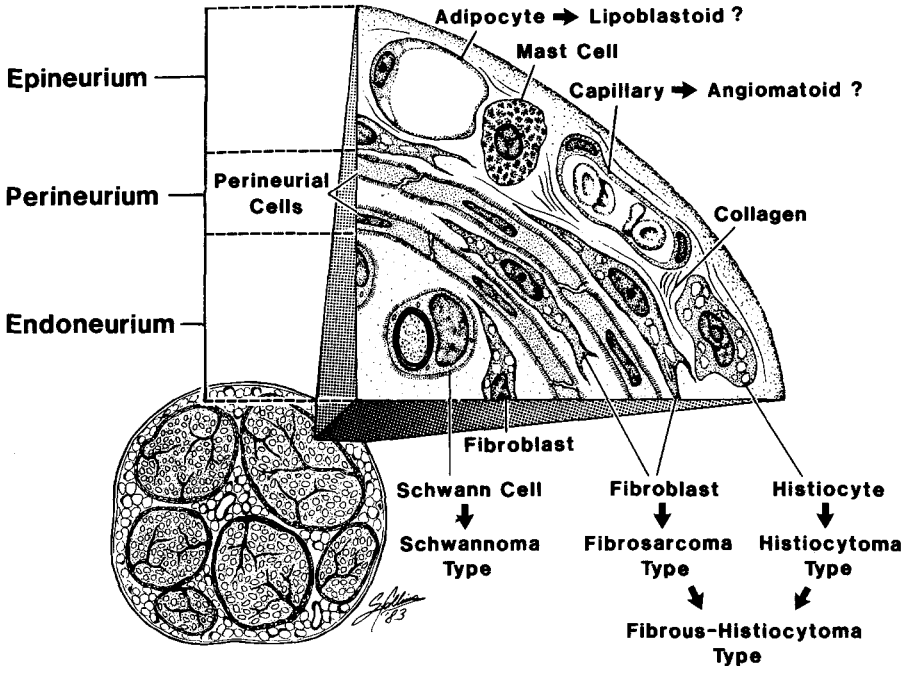

Fig. 10. Diagram illustrating the normal components of peripheral nerves. Peripheral nerve tumors could be derived from the various components of normal peripheral nerves, thus creating the different morphological manifestations that were observed in the cases presented in this article. Malignant proliferations of Schwann or perineural cells could give rise to the malignant schwannoma type of neurogenic sarcoma. Malignant neoplasms composed of proliferating fibroblasts or histiocytes or a mixture of both could account for the fibrosarcoma, histiocytoma and mixed fibrohistiocytoma types of neurogenic sarcomas

while the neurofibromas of Von Recklinghausen's disease become malignant in approximately 3–15% of the cases (D'Agostino et al. 1963; Robbins and Cotran 1979). If this is true, differences may be found in the behavior of these tumors as related to proliferating cell types. The present study documents the heterogenicity of these neurogenic sarcomas. It remains to correlate the different morphological expressions of these tumors with patient survival and prognosis, keeping in mind the possible role of different treatment modalities. The authors are currently investigating the association of specific morphologic types with the behavior of these neoplasms.

This ultrastructural study of thirteen neurogenic sarcomas arising in patients with Von Recklinghausen's disease confirms the heterogenous nature of these tumors, as well as the limited value of electron microscopy in establishing the neurogenic nature of these tumors. Most of the neoplasms examined represented malignant schwannomas, in spite of different light microscopic cellular patterns, some suggestive of other soft tissue neoplasms. The question remains whether these tumors are the result of the metaplastic ability of the Schwann cells or whether they originate from the different cellular components of normal peripheral nerves. The authors prefer the

last histogenetic hypothesis and agree with Erlandson and Woodruff (1982) that neurogenic sarcomas should probably be termed malignant peripheral nerve sheath tumors to emphasize their heterogeneous histogenetic nature. Only tumors with schwannian differentiation were found to be positive for S-100 protein. Subclassification of the neurogenic sarcomas, according to cell or origin, may prove to be clinically significant in the future in evaluating patient prognosis and perhaps in selecting types of therapy.

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