Virchows Arch [Pathol Anat] (1986) 409:433–451

Virchows Archiv A

Epithelioid malignant schwannoma

A study of 14 cases

Pär Lodding, Lars-Gunnar Kindblom, and Lennart Angervall
Department of Pathology II, University of Göteborg, Sahlgren Hospital, S-41345 Göteborg, Sweden

Summary. We report a light and electron microscopic, immunohistochemical, clinical and prognostic study of 14 patients with epithelioid malignant schwannoma. In 8 patients the tumour involved a major nerve. The tumours were rather small in most instances, the largest diameter being less than 5 cm in 7 cases. Light microscopically, they showed highly cellular areas of epithelioid, polygonal or rounded cells characteristically forming cords and rows and arranged in nodules of varying size. Spindle cell sarcoma areas as in classical malignant schwannoma were seen in 9 cases, and neurofibromatous areas in one case. Four cases were entirely epithelioid in appearance. Electron microscopically the epithelioid tumour cells showed nuclei with mostly even contours containing one or two trabecular or reticular nucleoli, cytoplasmic projections, intra-cytoplasmic myelin-like figures, intercellular junctions and discontinuous, sometimes multilayered external lamina material. The ultrastructural findings indicate that epithelioid malignant schwannoma is a tumour of neural crest derivation having features of Schwann cell differentiation. Immunohistochemically, S-100 protein was demonstrated in 7 tumours and neuron specific enolase in 3. There was a female predominance, 9/14, and a median age of 38.5 years (range 17–74). The extremities, including the hip and shoulder regions, were the most common sites, 12/14. The tumour proved highly malignant; 9 of 14 patients were dead at the time of follow-up and a high incidence of metastasis (7 of 14) was observed.

Key words: Malignant schwannoma – Electromicroscopy – Immunohistochemistry – S-100 protein – Neuronspecific enolase

Introduction

Most authors appear to have accepted the Schwann cell as the progenitor of malignant tumours of nerve sheath origin, and have therefore favored

Offprint requests to: P. Lodding at the above address

the term malignant schwannoma (Tsuneyoshi and Enjoji 1979; Chen et al. 1980; Taxy et al. 1981; Chitale and Dickersin 1983; Enzinger and Weiss 1983). However, Erlandson and Woodruff (1982) have maintained that these tumours may arise from either of the principal cells constituting the nerve sheath, the Schwann cells, perineurial cells, and fibroblasts, and have therefore recommended the descriptive term malignant peripheral nerve sheath tumour (PNST). The ability of malignant PNST to present areas with heterologous differentiation of both benign and malignant histological appearance, makes the definition and classification of these tumours more difficult. Examples are the presence of well-differentiated glandular structures (Schmincke 1956; Woodruff 1976; Krumerman and Stingle 1978; Warner et al. 1983; Uri et al. 1984), rhabdomyoblastic differentiation (so-called Triton tumour) (Woodruff et al. 1973), other types of sarcomatous differentiation (D'Agostino et al. 1963a, b; Ducatman and Scheithauer 1984) and melanocytic forms (Janzer and Makek 1983).

The term epithelioid malignant schwannoma has been applied to malignant tumours which consist of epithelioid areas which may resemble carcinoma or malignant melanoma. However, they can still be classified as malignant PNST, since they fulfil one or more of the traditional criteria of these tumours, i.e. association with peripheral nerves, neurofibromas or von Recklinghausen's neurofibromatosis. Moreover, areas with a spindled neurofibrosarcoma-like histological appearance may be present. Occasional tumours with these properties have been described previously (Stewart and Copeland 1931; Stout 1935; Gore 1952; McCormack et al. 1954; White 1971; Flossdorf et al. 1981; Chitale and Dickersin 1983; Weiss et al. 1983; Bojsen-Møller and Myhre-Jensen 1984; Enjoji and Hashimoto 1984). Their frequency among traditional malignant PNST has been estimated at 17% by Tsuneyoshi and Enjoji (1979), while Enzinger and Weiss (1983) have reported only 5%. We know of only one case of a proven malignant epithelioid schwannoma which has been thoroughly studied ultrastructurally (Alvira et al. 1976). This tumour showed some features consistent with Schwann cell differentiation, but lacked the typical cytoplasmic projections, and it was suggested that it had originated from the perineurial cell of the nerve sheath. In an unillustrated abstract, Chiu and Troster (1979) reported a case of epithelioid malignant schwannoma, which at electron microscopy showed large tumour cells, rich in mitochondria and cytoplasmic reticulum, and surrounded by often incomplete external lamina. Two epithelioid schwannomas without proven malignancy which were studied ultrastructurally appeared more differentiated, and revealed Schwann cell features (Taxy and Battifora 1981), as did one case of a well-differentiated malignant epithelioid schwannoma mentioned by Enzinger and Weiss (1983). The latter authors found that S-100 protein was present in 2 of 7 cases (Weiss et al. 1983). Since no series has previously been studied with follow-up, there is limited knowledge of the tumour's clinical course and prognosis.

The purpose of this investigation was to study a series of malignant epithelioid schwannomas by a clinical, light microscopic, ultrastructural and immunohistochemical analysis in order to further characterize and define

this rare soft tissue sarcoma. The present study was to further characterize and define malignant epithelioid schwannoma by a light microscopic, ultrastructural and immunhistochemical study of 14 cases, and to describe its clinical appearance and prognosis.

Material and methods

Material

From a review of a Swedish national series of soft tissue sarcomas reported to the Swedish Cancer Registry 1958–1971, and from the files at the Department of Pathology, Sahlgren Hospital, Göteborg, Sweden, a series of 14 cases of epithelioid malignant schwannoma was collected. Up to date clinical records, follow-up data and paraffin blocks from the surgical specimens were available in all 14 cases. Autopsies were performed on 5 of the 9 deceased patients and tissue blocks for microscopical review were available from 2 of them.

Methods

Light microscopy. 4–5 μm thick sections from paraffin-embedded tissue blocks were stained according to van Gieson and with haematoxylin and eosin. Silver impregnation according to Gordon and Sweet was used to demonstrate reticulin, Luxol fast blue staining to demonstrate myelin and Palmgren's silver impregnation to demonstrate axons. The periodic acid Shiff reaction (PAS) with and withour prior diastase (Merck, Darmstadt, FRG) digestion, was performed to demonstrate glycogen. The Masson-Fontana method was used for the demonstration of reducing pigment. Staining with Alcian blue at pH 2.5 and 1.0 was performed to identify glucosaminoglycans in cases where intercellular spaces contained mucosubstances. The tumours were graded on the basis of the degree of cellular polymorphism, cellularity and mitotic frequency, as described previously (Markhede et al. 1982; Merck 1983).

To estimate the mitotic activity, the number of mitoses was counted in 10 high power fields (HPF) chosen at random from each case, using objective ×25 and ocular ×10. The measurement of the visual field then made it possible to estimate the mitotic activity per mm^2. In tumours with both epithelioid and spindle-cell areas, the mitotic activity was estimated in both types of areas separately.

Immunohistochemistry. Rabbit antibovine S-100 protein and rabbit-antibovine neuronspecific enolase (NSE) were a gift from associate professor Kenneth Haglid and Dr. Lars Rosengren, Department of Histology, University of Göteborg. The procedure for purifying S-100 proteins and the production of the antisera has previously been described in detail (Angervall et al. 1984). The avidin-biotin complex (ABC) method was used as described in detail by Hsu and coworkers (1981). The working dilutions of the antisera which were used were chosen so that optimal staining of control tissues and the studied tumours was obtained, while background staining was minimal. The anti-S-100 serum was used in a 1:500 dilution, and the anti-NSE serum in a 1:1000 dilution. Malignant melanomas and peripheral nerves were used as control tissues for S-100 protein, while brain, peripheral nerves, ganglia, and carcinoids were used for NSE.

Electron microscopy. Fresh tissue from the surgical specimens was available in 6 cases (Nos. 1, 3, 5, 10, 13, 14). Small pieces of tissue from 3 of these tumours (Nos. 5, 10, 14) were initially fixed in 4% formaldehyde and were then washed in cold buffer, postfixed with 1% OsO_4 for 1 h, dehydrated in ethanol and embedded in Epon 812. In 3 cases (Nos. 1, 3, 13) the tissue was initially fixed in 2.5% glutaraldehyde in 0.1 M cacodylate buffer at pH 7.2 for 2–4 h at 4° C, then washed in cold buffer and subsequently processed as described above. Small selected pieces from the paraffin blocks from two cases (Nos. 2 and 4) were cut out, carefully deparaffinized in xylene, rehydrated in decreasing concentrations of alcohol, washed

in cacodylate buffer and fixed in 1% OsO_4. They were therafter dehydrated in ethanol, embedded in Epon and processed and examined as described above.

1 μm thick sections were made from the Epon blocks (5–20 from each case), and stained with toluidine blue. The sections were used to select representative areas of the tumour tissue with epithelioid appearance. Ultrathin sections were cut on an LKB Ultrotome, stained with uranyl acetate and lead citrate and examined in a Philips 400 electron microscope.

Results

Clinical data

The sex and age of the patients, the nature and duration of their symptoms, the anatomical location, size, and treatment of the tumours and follow-up data are listed in Table 1. In 8 cases the tumours clearly involved major nerve trunks at surgery. In one case the tumour involved a smaller non-defined nerve of the upper arm. The 8 major nerve structures engaged were the brachial plexus in three cases, the peroneal nerve in two cases, and the IInd intercostal nerve, the median nerve and the sciatic nerve in one case each. One patient (No. 11) had documented von Recklinghausen's neurofibromatosis. However, the remaining patients were not specifically examined or followed-up in terms of this desease.

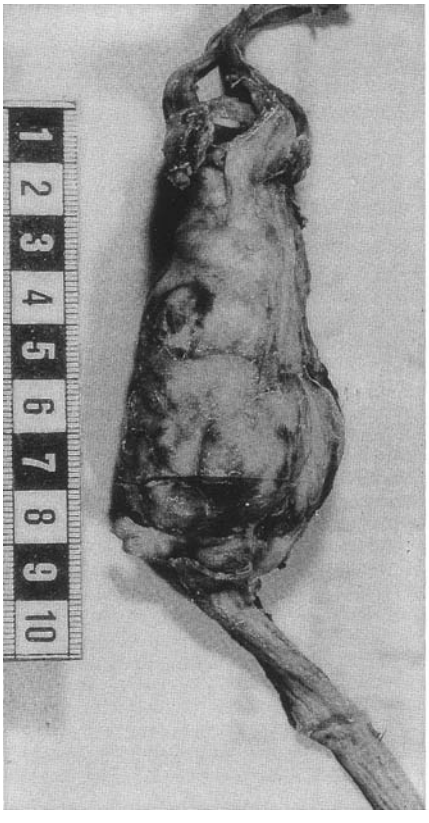
Three patients were alive without signs of tumour disease at follow-up, 1 to 5.5 years after diagnosis. Local recurrecnces occurred once in three cases. Nine patients had died from tumour. The lesions had metastasized in 7 cases, the lungs and/or the pleura being the most common site. Regional lymph node metastases were observed in three cases.

Gross examination

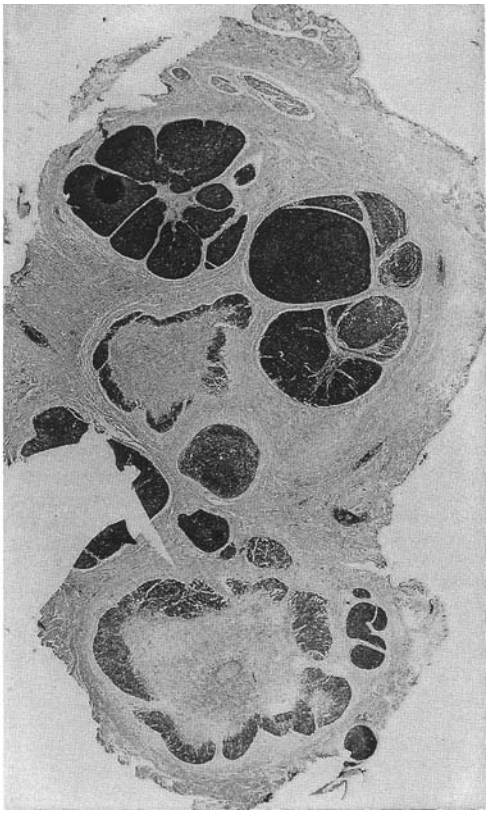
In 8 cases, the tumour was intimately associated with an identified nerve trunk or plexus, and with a small undefined nerve in one case. The tumours formed a fusiform mass, growing within and along the nerve (Fig. 1) except in one case where the mass was located in the left brachial plexus revealing a plexiform manner of growth (Fig. 2). All 14 tumours were firm and the cut surfaces were greyish-white in color, sometimes with necrotic and haemorrhagic areas. The largest diameter was less than 5 cm in 7 of the tumours, 5–10 cm in 5 and larger than 10 cm in two.

Light microscopic appearance

Highly cellular areas of epithelioid, polygonal or rounded cells were common to all the tumours. These cells often formed nodules of varying size (Fig. 3). Within these, the cells were arranged in narrow anastomizing cords and rows, which were sometimes separated by intercellular spaces containing mucosubstances (Figs. 4A and B). Four cases were entirely epithelioid in appearance (Nos. 1, 3, 9, 13). In all the other cases except one (No. 4), the epithelioid areas predominated, but there were also sarcomatous spindle-



1



2

Fig. 1. Case 3. Fusiform tumour mass growing within and along the sciatic nerve

Fig. 2. Case 2. Tumour within the left brachial plexus showing a plexiform manner of growth. The tumour tissue appears dark by the positive staining for S-100 protein. The paler central areas in two of the nodules correspond to benign-looking neurofibromatous areas. ×6

cell areas, and in one case (No. 2) neurofibroma-like areas. The epithelioid and spindle-cell areas were often sharply demarcated from one another (Fig. 3).

The epithelioid tumour cells had a primitive, moderately polymorphous appearance. They were mononuclear, containing a round or slightly oval vesicular nucleus, with a distinct nuclear membrane. The nuclei contained one or occasionally more distinct nucleoli. Thin bridges or line-like structures transversing the nuclei were observed. The generally abundant cytoplasm was amphopilic or slightly acidophilic, and the cells showed distinct cell membranes. True rosette formations were not observed.

The spindle cell areas varied in cellularity and degree of cellular and nuclear atypia within the same tumour and between different tumours. At least part of the spindle cell component appeared histologically malignant in all the tumours with spindle cell areas except one (No. 2). The cells

Table 1. Clinical data and follwo-up in 14 cases of malignant epithelioid schwannoma

Case no.	Sex	Duration of symptoms	Nature of symptoms	Age at diagnosis (ys)	Anatomical location	Size (cm)	Treatment location	Local recurrence	Follow-up	
									Duration	Course
1	M	1 year	Mass left upper arm, pain radiating to the left wrist and 1st and 3rd fingers of left hand	20	Proximal part of left median nerve	2,5 × 1	Local excision followed by amputation of left scapula and arm	none	5.5 years	Alive and no signs of tumour
2	F	3 months	Severe pain left armpit, radiating to neck and 3rd and 4th fingers of the left hand	74	Left brachial plexus	4 × 2	Local excision followed by wider do including nerve resection	1	18 years	Dead from myocardial infarction, no signs of tumour
3	F	1.5 months	Mass dorsal aspect of right thigh, right-sided S-1 syndrome	33	Proximal part of right sciatic nerve	10 × 4	Local resection of right sciatic nerve, followed by amputation of right leg	none	1.2 years	Dead, with extensive metastases to lungs, pleurae, liver, adrenals, pancreas, peritoneum and lymph nodes. Autopsy performed
4	F	4 years	Enlarging mass left buttock acute pains in lumbar and left gluteal area	33	Left gluteal muscles	11 × 6 × 5	Wide local excision	none	2 months	Dead, with extensive metastases to lungs, pleurae. liver, peritoneum and lymph nodes. Autopsy performed
5	M	11 years	Mass laterally right lower leg, pain radiating to right foot	40	Proximal part of right peroneal nerve	4 × 2.5 × 2	Local excision followed by amputation of right lower leg and resection of right sciatic nerve distal of hip	none	4 years	Alive and no signs of tumour disease
6	M	1 year	Pain, paresthesia and reduced sensitivity left upper arm	17	Left brachial plexus	7	Amputation of left arm	none	13 years	Dead, pulmonary and pleural metastases. No autopsy performed

7	F	1 year	Enlarging mass anterior aspect of left thigh	35	Left rectus femoris muscle	2.5	Local excision followed by wider do, radio- and chemotherapy	none	2.5 years	Dead, with pulmonary metastases. No autopsy performed
8	F	4 years	Mass posterior aspect of left knee, stiffness of knee joint	21	Left peroneal nerve, popliteal fossa	2.5 × 2	Wide local excision followed by radio- and chemotherapy	none	1.8 years	Dead, with pulmonary and pleural metastases. Autopsy performed
9	F	2 months	Mass right upper arm, paresthesia of right thumb	40	Between humerus and biceps muscle right arm, in connection to small nerve	3	Local excision followed by wider do	none	2 years	Dead, with pulmonary and pleural metastases. No autopsy performed
10	M	1 year	Enlarging mass right groin	61	Right inguum	4.5 × 3.5 × 2	Local excision followed by wider do, radio- and chemotherapy	none	10 months	Dead, with inguinal lymph node metastases. No autopsy performed
11[a]	M	1 year	Pains left shoulder region, left-sided Horner's syndrome	48	Left upper chestwall, second intercostal nerve	10	Local excision	1	1 year	Dead, with inoperable local recurrence constricting trachea and cervical vessels. Autopsy performed
12	F	2 months	Enlarging mass right side of abdomen	69	Abdominal wall and cavity	15	None	none	3 weeks	Dead from abdominal tumour and pulmonary embolia. Autopsy performed
13	F	3 months	Enlarging mass right lower leg	62	Distal part of right lower leg	9 × 5	Local excision followed by wider do	none	1 year	Alive and no signs of tumour
14	F	5 months	Enlarging mass right supra-clavicular fossa	37	Right brachial plexus	10	Local excision followed by radio- and chemotherapy	1	1 year	Large local recurrence after 3 years radically removed by extended thoraco-scapular amputation

[a] von Recklinghausen's neurofibromatosis.

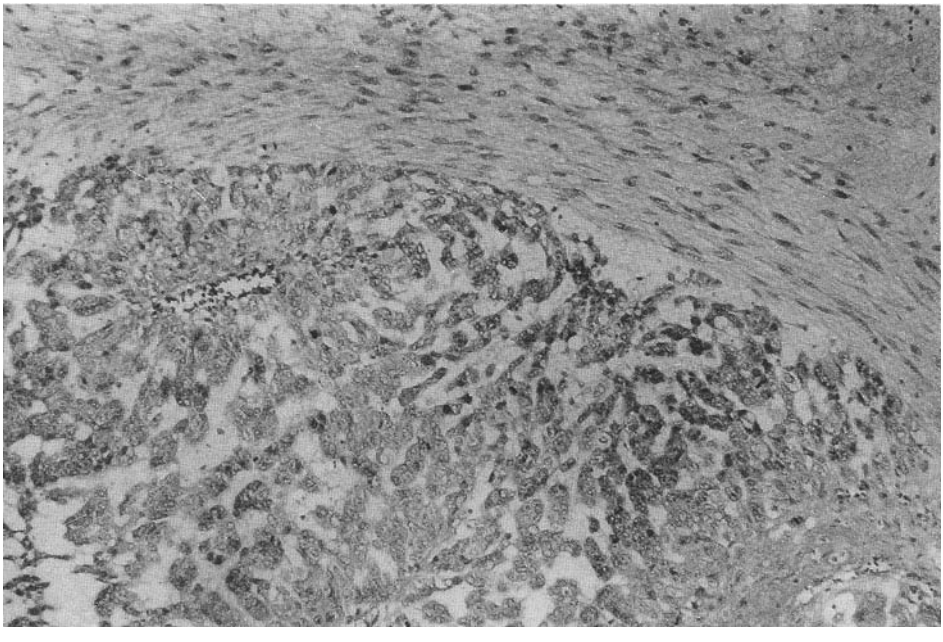
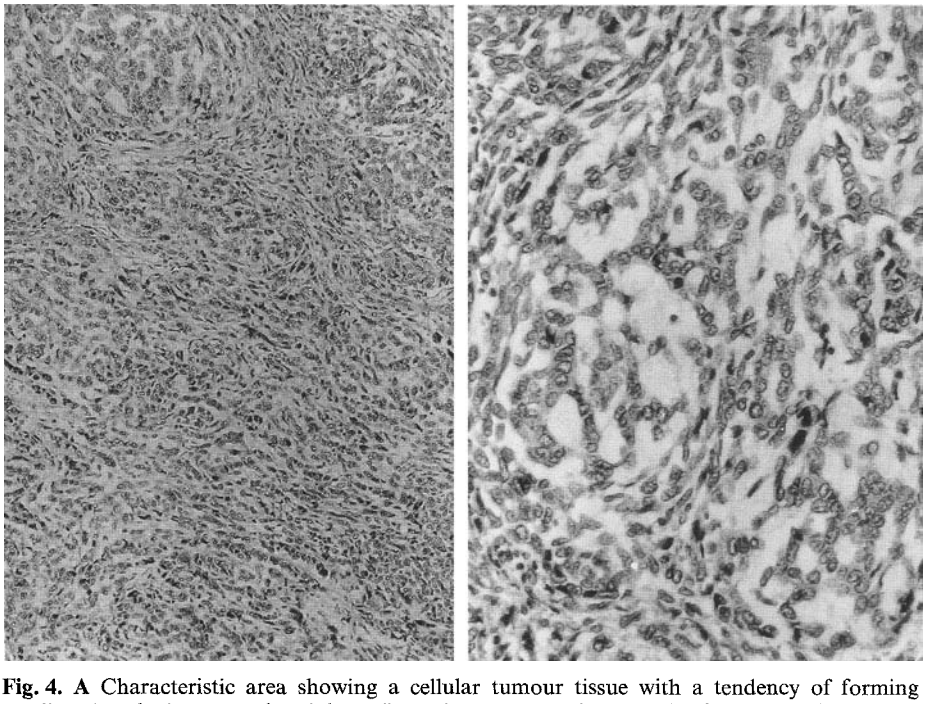


Fig. 3. Part of a nodule composed of epithelioid tumour cell forming anastomosing cords and rows, sharply demarcated from a spindle cell area. ×175, H & E



A **B**

Fig. 4. A Characteristic area showing a cellular tumour tissue with a tendency of forming small unsharply demarcated nodules. **B** Irregular anastomosing strands of tumour cells enclosed within mucosubstance: **A** ×100; **B** ×240, H & E

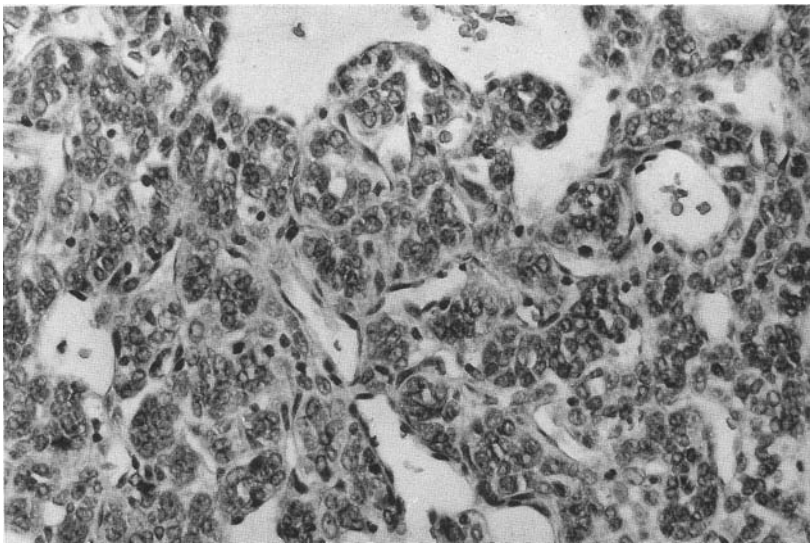


Fig. 5. Small nests of epithelioid tumour cells intimately associated with and protruding into thin-walled sinusoidal or capillary-like angulated vessels, creating a pericytoma-like appearance. ×240, H & E

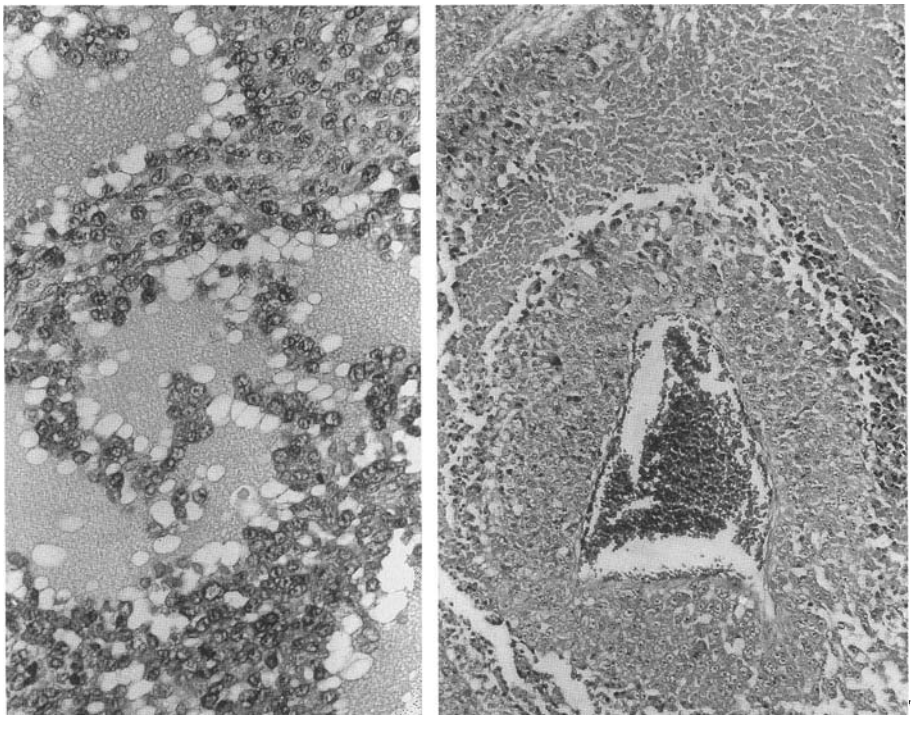
had elongated, moderately hyperchromatic nuclei, often with pointed ends. The amphophilic cytoplasm appeared homogeneous, with mostly indistinct cell membranes. In case 2, which had a plexiform manner of growth within large nerve trunks of the brachial plexus, areas within the tumour had the appearance of a neurofibroma, without noteworthy atypia.

The estimated median mitotic activity per mm^2 was 8 (range 2–75) in the epithelioid components of the tumours and 4 (range 2–25) in the histologically malignant spindle-cell areas of the tumours. Atypical mitotic figures were few. The epithelioid areas of all tumours were of high grade malignancy (grade III–IV).

The intraneural tumour growth observed at gross examination was verified microscopically in all instances. In 7 of these 9 tumours there was also extraneural growth, occasionally with diffuse infiltration of surrounding adipose tissue and skeletal muscle.

The tumour tissue generally appeared highly vascular. The majority of tumour vessels were delicate and capillary-like. Larger, angulated vessels were also seen, sometimes reaching a width of 5 mm. These were mostly lined by a single layer of flattened endothelial cells. Occasional sinusoid-like vessels without apparent endothelial lining were also seen. A pericytoma-like pattern was prominent in one case (Fig. 5). Occasionally, tumour cells formed narrow cords and rows concentrically arranged around wide thin-walled tumour vessels. One case showed a prominent polling phenomenon (Fig. 6). A few glandular formations appeared in a small epithelioid area in one of the cases.

Areas of necrosis were seen in all cases; these were often extensive and



6

Fig. 6. Tumour area containing pools filled with fluid. × 240, H & E

Fig. 7. Necrotic tumour area with an island of viable tissue arranged around a thin-walled tumour vessel. × 100, H & E

formed garland-like, sharply demarcated patterns. Characteristically, islands of viable tumour tissue arranged around thin-walled vessels appeared within the extensive necrotic areas (Fig. 7). Collections of foam cells were common, with or without association with necrosis.

Metastases to regional lymph nodes were observed in three cases. All of these metastases were entirely epithelioid in appearance, corresponding well to the epithelioid counterpart of the primary tumour. Metastases to other organs, such as the lungs and liver, showed a more varied histology, featuring both epithelioid and spindle-cell areas. In one case (No. 8), there was cartilage formation within a pulmonary metastasis, which consisted predominantly of spindle-shaped tumour cells.

Four cases showed a weak PAS-positive diastase-digestible granular staining of the cytoplasm of the tumour cells, indicating the presence of glycogen. A prominent network of reticulin could be seen, mostly separating groups of tumour cells, or in some areas individual cells in silver impregnated sections. A weak Alcian blue staining at pH 2.5 of the intercellular matrix was noted in some areas, but there was no positive staining at pH 1.0, and sulphated glucosaminoglycans were thus not demonstrated. Myelin and

axons were revealed by Palmgren's silver impregnation and Luxol fast blue respectively only in normal nerve trunks and nerve fascicles enclosed within the tumour. Masson-Fontana's stain did not demonstrate reducing pigment in any of the cases.

Immunohistochemistry

Seven tumours stained positively for S-100 protein. Only case 2, which was a plexiform lesion, showed a strongly positive, evenly dispersed staining in the vast majority of the tumour cells (Fig. 2). In 3 cases (Nos. 1, 4, 13) staining was only seen in limited groups of tumour cells, of both epithelioid and spindle-cell character. In two cases (Nos. 6, 12), there was staining of a minority of cells evenly dispersed within both epithelioid and spindle-cell areas of the tumours. In one case (No. 11) positive staining was confined to groups of spindle-shaped cells, the epithelioid areas being entirely negative. Three tumours were positively stained for NSE (Nos. 2, 4, 12), all of which were also positive for S-100 protein. Of these, case 2 was strongly NSE-positive in almost all cells, while the other cases showed positivity for NSE in groups of cells. Nerves in the sections stained for NSE and S-100 protein served as intrinsic controls and were strongly positively stained in all cases. NSE positivity appeared to be located mainly in and along the axons, whereas S-100 protein positivity was located at the periphery of, and alongside the axons, within Schwann cells.

Ultrastructural appearance

In 6 of the tumours the nuclei were round or oval, with even contours (Fig. 8), while two tumours showed nuclei which were strongly clefted, giving rise to cytoplasmic pseudoinclusions. The nuclei contained one or, on rare occasions, two nucleoli which were usually trabecular or reticular. The nucleoli often eccentrically located, varied considerably in size, having a diameter half of that of the nucleus at the most.

The abundant cytoplasm was richly endowed with organelles, especially mitochondria and endoplasmic reticulum. The endoplasmic reticulum was predominantly of granular type (RER), and arranged in stacks of parallel membranes. There were tumour cells with RER forming wide cisternae, filled with a grey-staining granular material, in all cases. Numerous polysomes and large groups of free ribosomes were common findings. Well-developed Golgi zones were encountered on rare occasions. Lipid droplets, lysosome-like bodies and, on rare occasions, larger phagosomes were found within single scattered cells. Glycogen was abundant within some tumour cells in one case. In 6 of the 8 cases some tumour cells contained multilayered membrane structures, which when densely packed resembled so-called myelin figures. Occasionally, groups of several centrioles were seen. Some of these appeared closely associated with the cytoplasmic membrane and at the base of cytoplasmic extensions, giving them a cilium basal body-like appearance. Mostly, sparse amounts of randomly distributed filaments of

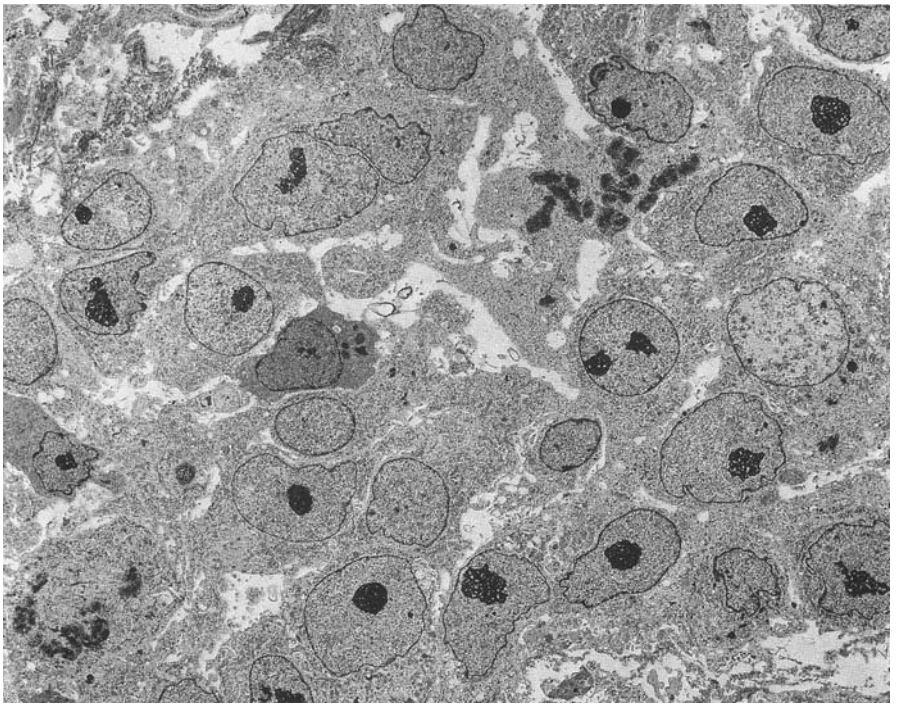


Fig. 8. Characteristic area showing rather closely associated tumour cells with abundant cytoplasm and a rounded or oval nucleus with even contours and a thin rim of peripheral heterochromatin and a prominent nucleolus. Two mitotic figures are seen. × 1,650

intermediary type (8–12 nm) were observed, but scattered cells contained abundance of such filaments and also some microtubules. There were also cells with thin cytoplasmic filaments arranged in parallel peripherally. Slender, interdigitating cytoplasmic projections (Fig. 9A), sometimes containing bundles of such thin filaments, were observed in most tumours (Fig. 9B). Large axon-like cytoplasmic extensions enclosed by one or more surrounding tumour cells were noted in two cases. In cross section these structures appeared light-staining and were poor in organelles, containing filaments, microtubuli, sparse amounts of small mitochondria and polysomes (Fig. 10). They contained no endoplasmic reticulum, and were not invested by an external lamina. In 6 cases there were tumour cells surrounded by a mostly discontinuous, sometimes multilayered external lamina (Fig. 11A). Groups of cell junctions, of gap junction, tight junction and desmosome-like types, were noted between intimately associated tumour cells in 4 cases (Fig. 11B). Groups of cells were enclosed within a rather dense intercellular matrix, which often had a fibrillary texture, containing relatively small amounts of collagen of ordinary appearance. In two cases, so-called long-spacing collagen (Luse bodies) was observed.

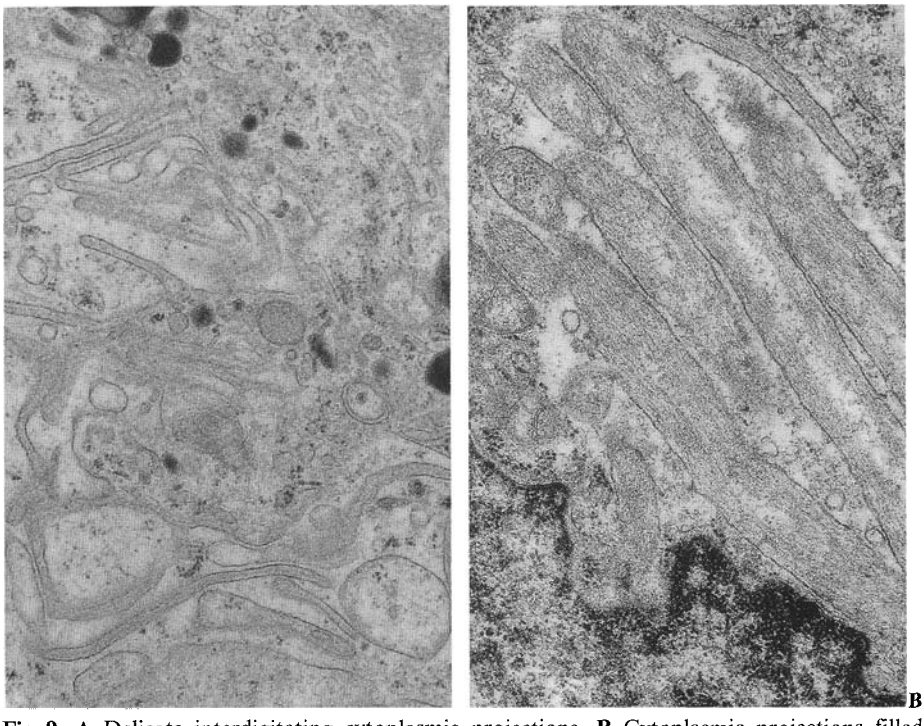


Fig. 9. **A** Delicate interdigitating cytoplasmic projections. **B** Cytoplasmic projections filled with bundles of thin filaments. **A, B** × 22,500

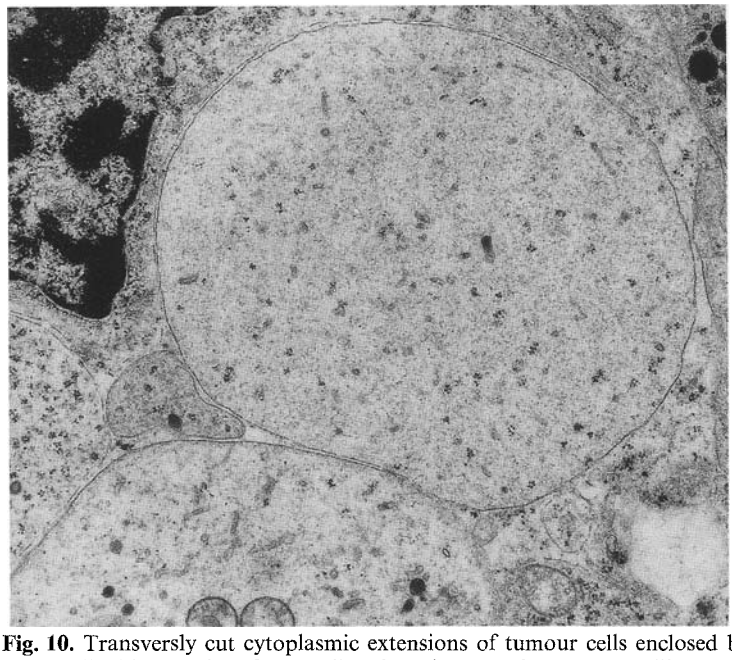


Fig. 10. Transversly cut cytoplasmic extensions of tumour cells enclosed by neighbouring tumour cells. The paucity of organelles gives the extensions an axon-like appearance. × 14,000

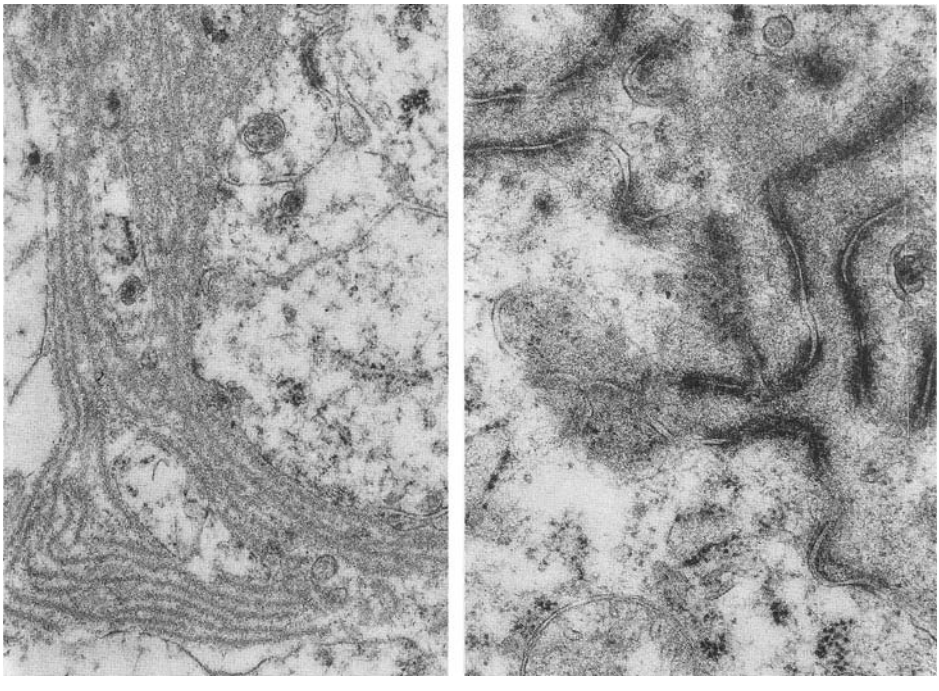


Fig. 11. A Multilayered external lamina surrouonding a tumour cell. **B** Tumour cells connected by numerous cell junctions of varying appearance. A ×26,000; B ×37,000

Discussion

A characteristic light-microscopic feature of the tumours in the present series was epithelioid cells arranged in rows and cords and forming nodules. All cases except 4 (Nos. 1, 3, 9, 13) showed either sarcomatous spindled areas as found in ordinary malignant PNST, or neurofibroma-like structures. The growth within one ore more nerves in 9 of the 14 cases further indicates the peripheral nerve origin of this tumour. In 4 of the 5 tumours without proven growth in nerves, the immunohistochemical and/or ultrastructural study supported a Schwann cell differentiation. In the fifth case, in which electron microscopy was not performed, the tumour had a nodular and epithelioid appearance light microscopically, as well as spindle-cell areas as in ordinary malignant PNST. Thus, in all the 14 tumours there were evidence of a malignant peripheral nerve sheath tumour with epithelioid features. Four of the tumours, however, revealed each some diverging features not shared by the other tumours of the series. One of them (Case 14) contained areas in which groups of epithelioid tumour cells and numerous thin-walled angulated vessels gave a haemangiopericytoma-like appearance. This tumour otherwise shared the light microscopic characteristics of the other tumours, and also contained spindled sarcomatous areas. Futhermore, the tumour originated from the brachial nerve plexus and revealed ultrastructural features indicating a Schwann cell differentiation. It is well known

that pericytoma-like patterns may appear in various types of soft tissue sarcomas (Enzinger and Weiss 1983).

The presence of pools of fluid containing a few or no cells within solid areas was a prominent feature in areas of one of the tumours (Case 13), a phenomenon which can be seen in extraskeletal Ewing's sarcoma (Angervall and Enzinger 1975). However, the tumour otherwise differed from Ewing's sarcoma by its light- and electron microscopic appearance.

One tumour (Case 2), growing within the brachial nerve plexus, revealed a prominent plexiform growth pattern with several of the nerve fascicles involved either by tumour tissue or a benign-looking neurofibroma-like tissue. Otherwise this case did not differ light-microscopically from the other cases and revealed a strong positive staining for S-100 protein and tumour cells positively stained for NSE. The light microscopic findings suggest that the tumour originated from a plexiform neurofibroma.

In one case there were a few glandular structures within epithelioid areas with otherwise typical arrangement of the tumour cells in cords and rows, indicating the relationship between epithelioid malignant schwannoma and malignant schwannoma with glandular differentiation (Woodruff 1976; Uri et al. 1984), another subtype of malignant PNST.

Seven of the 8 tumours studied ultrastructurally had some features of Schwann cell differentiation. Such features included delicate interdigitating filament containing cytoplasmic projections, intracytoplasmic myelin-like figures, intercellular junctions, discontinuous, sometimes multilayered external lamina and the presence of long-spacing collagen, all of which have been described in both benign (Waggener 1966; Erlandson and Woodruff 1982) and malignant PNST of supposed Schwann cell origin (Chiu and Troster 1979; Tsuneyoshi and Enjoji 1979; Chen et al. 1980; Taxy et al. 1981; Erlandson and Woodruff 1982; Chitale and Dickersin 1983; Enzinger and Weiss 1983). The axon-like cytoplasmic tumour cell projections noted in two cases can be an expression of nerve cell differentiation. However, it is wellknown that Schwann cells regenerating after nerve damage may form similar axon-like projections (Morris et al. 1972). In one case (No. 2) ultrastructural features of Schwann cell differentiation were not found, but in this case the material obtained from paraffin embedded tissue was of poor quality, making detailed analysis impossible. A further observation of interest was the presence of multiple centrioles, occasionally peripherally located in association with cytoplasmic projections, giving them a cilium basal body-like appearance. Cilia have previously been observed in both ordinary and regenerating Schwann cells (Morris et al. 1972).

The light- and electron microscopic examination and the immunohistochemical analysis indicate that epithelioid malignant schwannoma is a primitive neuroectodermal tumor, which may at least partly display Schwann cell differentiation, and possibly nerve cell differentiation. In our series of epithelioid malignant schwannoma, there were both epithelioid and spindle-cell areas with tumour cells positive for both S-100 protein and NSE. The occurrence of both Schwann cell differentiaton and nerve cell differentiation, including neuroendocrine cell differentiation, has previously been described

in malignant PNST of predominantly spindle-cell type (Tsuneyoshi and Enjoji 1979; Warner et al. 1983).

The present series of epithelioid malignant schwannoma show some resemblance to peripheral neuroepithelioma (peripheral neuroblastoma, peripheral neuroectodermal tumour), a rare, primitive neuroectodermal tumour arising from peripheral non-autonomic nerves, which is characterized histologically by a neuroblastoma-like appearance and rosette formations (Harkin and Reed 1969; Harper et al. 1981; Enzinger and Weiss 1983; Gonzales-Crussi et al. 1984). Three such tumours studied immunohistochemically were found to be positive for both S-100 protein and NSE (Gonzales-Crussi et al. 1984). On rare occasions, neural tumours may show features of both neurofibrosarcoma (spindle cell malignant schwannoma) and neuroepithelioma (Enzinger and Weiss 1983). Neurofibrosarcomas also occasionally show rosette formations (Enzinger and Weiss 1983). Thus primitive neuroectodermal tumours originating from peripheral nerves may show varying degrees and directions of neuroectodermal cell differentiation. The epithelioid malignant schwannomas of the present series could be distinguished from peripheral neuroepithelioma since they revealed no neuroblastoma-like appearance and lacked rosette formations. Moreover, neurosecretory granules, present in neuroepithelioma (Enzinger and Weiss 1983) were not observed in any of the cases.

The presence in most cases of spindle-cell areas with a fascicular pattern, the immunohistochemical evidence of neuroectordermal cell differentiation in half the cases and the electron microscopic appearance without signs of epithelial differentiation help to distinguish epithelioid malignant schwannoma from carcinoma. Melanocytic differentiation may appear in peripheral nerve tumours (Mennemeyer et al. 1979; Burns et al. 1983; Janzer and Makek 1983; Font and Truong 1984; Krausz et al. 1984). In our series, reducing pigment such as melanin was not found light microscopically in any case, and melanosomes or premelanosomes were not found in any of the 8 cases studied ultrastructurally. Thus, the results of the morphological and immunohistochemical analysis are not consistent with a carcinoma or malignant melanoma. Furthermore, none of the patients followed up presented any other primary tumours which could have raised the possibility that the lesions represented metastases of a carcinoma or melanoma.

The sex and age distribution agrees with previous reports of ordinary malignant schwannoma (D'Agostino et al. 1963a; Tsuneyoshi and Enjoji 1979; Trojanowski et al. 1980; Enjoji and Hashimoto 1984). All tumours were deeply located within the soft tissues and showed a marked prediliction for the extremities. This distribution is in accordance with previously published series of malignant PNST, which have revealed the extremities to be the most common site, especially in patients without von Recklinghausen's neurofibromatosis (Gosh et al. 1973; Tsuneyoshi and Enjoji 1979). The tumours in the present series were relatively small for soft tissue sarcomas, half of them being less than 5 cm in largest diameter. In two series of deep soft tissue sarcoma only 10% (Markhede et al. 1982) and 18% (Rydholm et al. 1984), respectively, of the tumours were less than 5 cm

in largest diameter, figures corresponding well with those given in series of malignant PNST of ordinary type (Gosh et al. 1973; Guccion and Enzinger 1979). It can be noted that only one patient (No. 11) presented evident clinical findings of von Recklinghausen's neurofibromatosis. This may indicate that the incidence of von Recklinghausen's neurofibromatosis in patients with epithelioid malignant schwannoma is lower than that of ordinary malignant PNST, which has been reported as being between 26 and 67 per cent (White 1971; Gosh et al. 1973; Tsuneyoshi and Enjoji 1979). Guccion and Enzinger (1979) observed only 2 malignant schwannomas with a partly epithelioid appearance (5%) in a series of 46 malignant schwannomas occurring in patients with von Recklinghausen's neurofibromatosis, while Tsuneyoshi and Enjoji (1979) found 6 malignant PNST of epithelioid type (17%) in a study of 35 patients with malignant PNST who were not selected on the basis of von Recklinghausen's neurofibromatosis.

Histologically, all 14 tumours were highly malignant (grade III–IV), and out of the 11 patients who were followed up for more than 5 years, 9 had died of tumour. Metastatic spread was the main cause of death in 7 of them. Metastasis mainly occurred as a result of haematogenic spread to lungs, pleurae and liver, a pattern common in ordinary malignant PNST (White 1971; Ghosh et al. 1973; Guccion and Enzinger 1979; Tsuneyoshi and Enjoji 1979; Storm et al. 1980). It has earlier been emphasized that lymph node metastasis is a very rare occurrence in malignant PNST (Stout 1949; Vieta and Pack 1951; Das Gupta and Brasfield 1970; Guccion and Enzinger 1979). In our series of epithelioid malignant schwannoma, however, three of the patients with metastasizing tumours also had lymph node metastases. One case of malignant schwannoma with epithelioid features reported by Stout (1935) and another by McCormack and co-workers (1954) developed lymph node metastases.

The low incidence of local recurrence in this series (3/14), compared with that of series of malignant PNST (White 1971; Guccion and Enzinger 1979; Tsuneyoshi and Enjoji 1979), is probably due to the fact that 11 patients (all except Cases 11, 12 and 14) underwent a radical excision, performed in 7 instances by an orthopaedic surgeon with special skill and experience in the surgical treatment of soft tissue sarcomas[1]. It would thus appear that radical removal of the tumour is the surgical treatment of choice. In Stener's series of primarily radically operated soft tissue sarcomas of different types and malignancy grades, including malignant schwannomas, the local recurrence rate was 6.6 per cent (Markhede et al. 1982). Despite the low rate of local recurrence in the present series, the rate of metastasis was still high, and the prognosis was poor. The interpretation of this result is that the prognosis depends more on the high malignancy of the tumour than on the occurrence of local recurrence. Since radiotherapy and chemotherapy was initiated in three of four patients at an advanced stage of the tumour disease, the effect of such therapies cannot be evaluated from this series.

1 Professor B. Stener, Department of Orthopedic Surgery, Sahlgren Hospital, Göteborg, Sweden

References

Alvira MM, Mandybur TI, Menefee MG (1976) Light microscopic and ultrastructural observations of a metastasizing malignant epithelioid schwannoma. Cancer 38:1977–1982

Angervall L, Enzinger FM (1975) Extraskeletal neoplasm resembling Ewing's sarcoma. Cancer 36:240–251

Angervall L, Kindblom L-G, Haglid K (1984) Dermal nerve sheath myxoma; a light and electron microscopic, histochemical and immunohistochemical study. Cancer 53:1752–1759

Bojsen-Møller M, Myhre-Jensen O (1984) A consecutive series of 30 malignant schwannomas; survival in relation to clinico-pathological parameters and treatment. Acta pathol microbiol immunol scand (Sect A) 92:147–155

Burns DK, Silva FG, Forde KA, Mount PM, Clark HB (1983) Primary melanocytic schwannoma of the stomach; evidence of dual melanocytic and schwannian differentiation in an extra-axial site in a patient without neurofibromatosis. Cancer 52:1432–1441

Chen KTK, Latorraca R, Fabich D, Padgug A, Hafez GR, Gilbert EF (1980) Malignant schwannoma; a light microscopic and ultrastructural study. Cancer 45:1585–1593

Chiu HF, Troster M (1979) Ultrastrucuture of malignant schwannomas (Abstr). Lab Invest 40:246

Chitale AR, Dickersin GR (1983) Electron microscopy in the diagnosis of malignant schwannomas; a report of six cases. Cancer 51:1448–1461

Chung EB, Enzinger FM (1983) Malignant melanoma of soft parts; a reassessment of clear cell sarcoma. Am J Surg Pathol 7:405–413

D'Agostino AN, Soule EH, Miller RH (1963a) Primary malignant neoplasms of nerves (malignant neurilemomas) in patients without manifestations of multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1003–1014

D'Agostino AN, Soule EH, Miller RH (1963b) Sarcomas of the pripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer 16:1015–1027

Das Gupta TK, Brasfield RD (1970) Solitary malignant schwannoma. Ann Surg 171:419–428

Dhillon AP, Rode J, Leathem A (1982) Neurone specific enolase: an aid to the diagnosis of melanoma and neuroblastoma. Histopathology 6:81–92

Ducatman BS, Scheithauer BW (1984) Malignant peripheral nerve sheath tumours with divergent differentiation. Cancer 54:1049–1057

Enjoji M, Hashimoto H (1984) Diagnosis of soft tissue sarcomas. Path Res Pract 178:215–226

Enzinger FM, Weiss SW (1983) Malignant tumors of peripheral nerves. In: Soft Tissue Tumors, The CV Mosby Co., St. Louis; pp 625–656

Erlandson RA, Woodruff JM (1982) Peripheral nerve tumors: an electron microscopic study of 43 cases. Cancer 49:273–287

Flossdorf R, Reinhardt V, Gerhard L (1981) Morphological studies in malignant tumors of the peripheral nervous system (neurofibrosarcoma, malignant schwannoma, Schwann cell sarcoma). Acta Neuropathol (Berl) suppl VII, 129–133

Font RL, Truong LD (1984) Melanotic schwannoma of soft tissues; electron-microscopic observations and review of literature. Am J Surg Pathol 8:129–138

Ghosh BC, Ghosh L, Huvos AG, Fortner JG (1973) Malignant schwannoma; a clinicopathologic study. Cancer 31:184–190

Gonzalez-Crussi F, Wolfson SL, Misugi K, Nakajima T (1984) Peripheral neuroectodermal tumors of the chest wall in childhood. Cancer 54:2519–2527

Gore I (1952) Primary malignant tumors of nerve; a report of eight cases. Cancer 5:278–296

Guccion JG, Enzinger FM (1979) Malignant schwannoma associated with von Recklinghausen's neurofibromatosis. Virchows Arch (Path Anat Histol) 383:43–57

Harkin JC, Reed RJ (1969) Tumors of the peripheral nervous system. In: Atlas of tumor pathology, second series, fasc 3, Washington DC, Armed Forces Insititute of Pathology

Harper PG, Pringle J, Souhami RL (1981) Neuroepithelioma – a rare malignant peripheral nerve tumor of primitive origin: report of two cases and a review of the literature. Cancer 48:2282–2287

Hsu S-M, Raine L, Fanger H (1981) Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: a comparison between ABC and unlabeled antibody (PAP) procedures. J Histochem Cytochem 29:577–580

Janzer RC, Makek M (1983) Intraoral malignant melanotic schwannoma; ultrastructural evidence for melanogenesis by Schwann's cells. Arch Pathol Lab Med 107:298–301
Krausz T, Azzopardi JG, Pearse E (1984) Malignant melanoma of the sympathetic chain; with a consideration of pigmented nerve sheath tumours. Histopathology 8:881–894
Krumerman MS, Stingle W (1978) Synchronous malignant glandular schwannomas in congenital neurofibromatosis. Cancer 41:2444–2451
Markhede G, Angervall L, Stener B (1982) A multivariate analysis of the prognosis after surgical treatment of malignant soft-tissue tumors. Cancer 49:1721–1733
McCormack LJ, Hazard JB, Dickson JA (1954) Malignant epithelioid neurilemoma (schwannoma). Cancer 7:725–728
Mennemeyer RP, Hammar SP, Tytus JS, Hallman KO, Raisis JE, Bockus D (1979) Melanotic schwannoma; clinical and ultrastructural studies of three cases with evidence of intracellular melanin synthesis. Am J Surg Pathol 3:3–10
Merck C (1983) Myxofibrosarcoma. Thesis, University of Göteborg, Göteborg, Sweden.
Morris JH, Hudson AR, Weddell G (1972) A study of degeneration and regeneration in the divided rat sciatic nerve based on electron microscopy. II. The development of the "regenerative unit". Z Zellforsch 124:103–130
Rydholm A, Berg NO, Gullberg B, Thorngren K-G, Persson BM (1984) Epidemiology of soft-tissue sarcoma in the locomotor system; a retrospective popultion-based study of the inter-relationships between clinical and morphological variables. Acta pathol microbiol immunol (Sect A) 92:363-374
Schmincke A (1956) In: Lubarsch O, Henke F, Rössle R (Eds) Handbuch der speziellen pathologischen Anatomie und Histologie. Band XIII/4 Erkrankungen des zentralen Nervensystems IV. Springer Verlag, Berlin-Göttingen-Heidelberg, p. 686
Stewart FW, Copeland MM (1931) Neurogenic sarcoma. Am J Cancer 15:1235–1320
Storm FK, Eilber FR, Mirra J, Morton DL (1980) Neurofibrosarcoma. Cancer 45:126–129
Stout AP (1935) The malignant tumors of the peripheral nerves. Am J Cancer 25:1–36
Stout AP (1949) Tumours of the peripheral nervous system. In: Atlas of tumor pathology, Section II, Fasc 6, Washington DC, Armed Forces Institute of Pathology
Taxy JB, Battifora H, Trujillo Y, Dorfman HD (1981) Electron microscopy in the diagnosis of malignant schwannoma. Cancer 48:1381–1391
Taxy JB, Battifora H (1981) Epithelioid schwannoma: Diagnosis by electron microscopy. Ultrastructural Pathology 2:19–24
Trojanowski JQ, Kleinman GM, Proppe KH (1980) Malignant tumors of nerve sheath origin. Cancer 46:1202–1212
Tsuneyoshi M, Enjoji M (1979) Primary malignant peripheral nerve tumors (malignant schwannomas); a clinicopathologic and electron microscopic study. Acta Path Jap 29:363–375
Uri AK, Witzleben CL, Raney RB (1984) Electron microscopy of glandular schwannoma. Cancer 53:493–497
Vieta JO, Pack GT (1951) Malignant neurilemomas of peripheral nerves. Am J Surg 82:416–431
Waggener JD (1966) Ultrastructure of benign peripheral nerve sheath tumors. Cancer 19:699–709
Warner TFCS, Louie R, Hafez GR, Chandler E (1983) Malignant nerve sheath tumor containing endocrine cells. Am J Surg Pathol 7:583–590
Weiss SW, Langloss JM, Enzinger FM (1983) Value of S-100 protein in the diagnosis of soft tissue tumors with particular reference to benign and malignant Schwann cell tumors. Lab Invest 49:299–308
White HR Jr (1971) Survival in malignant schwannoma; an 18-year study. Cancer 27:720–729
Woodruff JM (1976) Peripheral nerve tumors showing glandular differentiation (glandular schwannomas). Cancer 37:2399–2413
Woodruff JM, Chernik NL, Smith MC, Millett WB, Foote FW Jr (1973) Peripheral nerve tumors with rhabdomyosarcomatous differentiation (malignant "Triton" tumors). Cancer 32:426–439

Accepted March 25, 1986