Virchows Arch. A Path. Anat. and Histol. 383, 43–57 (1979)

Virchows Archiv A

Malignant Schwannoma Associated With Von Recklinghausen's Neurofibromatosis*

John G. Guccion and Franz M. Enzinger

Armed Forces Institute of Pathology, Laboratory Service, Veterans Administration Medical Center, and Department of Pathology, George Washington University School of Medicine, Washington, D.C., USA

Summary. A series of 46 malignant schwannomas occurring in soft parts of patients having von Recklinghausen's neurofibromatosis was analyzed. The diagnosis of malignant schwannoma was based upon the occurrence of malignant spindled cells closely resembling Schwann cells in the neoplasm and the close association or origin of the malignant schwannoma in a neurofibroma (27 tumors), or a large peripheral nerve (31 tumors). Additional histologic features useful in making the diagnosis of malignant schwannoma included the arrangement of the spindled tumor cells in a whorled pattern about thin-walled, gaping blood vessels, perivascular cellular proliferation and the presence of prominent myxoid stroma containing abundant hyaluronidase-sensitive acid mucopolysaccharides. Nuclear palisading was present in only one case. Eight tumors containing both neoplastic Schwann cells and rhabdomyoblasts and five containing both neoplastic Schwann cells and rhabdomyoblasts (malignant "Triton" tumors) and five containing foci of malignant cartilage cells were included in the series. The neoplasms occurred principally in adults (median age, 34 years) and were most common in the lower extremity (18 cases) and retroperitoneum (11 cases). A mass with or without pain was the most common presenting symptom (28 cases). The median size of excised tumors was 11 cm. The malignant schwannomas were highly malignant neoplasms, causing the death of 39 patients within five years and two patients within 6–10 years after diagnosis. Only four patients were alive and free of tumor 5–15 years after diagnosis.

Key words: Neurofibroma – Neurofibromatosis – Sarcoma.

Introduction

Although several extensive pathologic studies of malignant schwannoma have been reported (D'Agostino et al., 1963; D'Agostino et al., 1963; Ghosh et al., 1973; Harkin and Reed, 1968; White, 1971), definitive histologic criteria for

* Dedicated to Professor E. Uehlinger on the occasion of his 80th birthday

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Send offprint requests to: Prof. Dr. F.M. Enzinger, Armed Forces Institute of Pathology, Washington, D.C. 20306, USA

0340-1227/79/0383/0043/$03.00

the diagnosis of malignant schwannoma have not been readily apparent and this diagnosis has rested largely on the apparent origin of a malignant spindle cell neoplasm in a nerve or a neurofibroma. As a result, pathologists have continued to encounter difficulty in classifying spindle cell sarcomas as malignant schwannoma. Furthermore, clear correlation of gross and microscopic pathologic findings with the course of the disease has not been attained.

In this study, emphasis was given to the histologic diagnosis of malignant schwannoma, particularly to its morphologic distinction from other spindle cell sarcomas and to the correlation of various morphologic parameters with clinical behavior. Forty-six malignant schwannomas occurring in the soft parts of patients having von Recklinghausen's neurofibromatosis were analyzed in this study.

Materials and Methods

The gross and microscopic features, clinical data, and follow-up information on 46 malignant schwannomas occurring in soft parts of patients having neurofibromatosis in the files of the Armed Forces Institute of Pathology (AFIP) were reviewed and analyzed. In each of these hematoxylin and eosin (H & E) preparations were examined. In selected cases, the following staining techniques were utilized: Masson's trichrome stain, the periodic acid-Schiff (PAS) preparation with and without diastase digestion, the Mowry modification of the colloidal iron stain for acid mucopolysaccharide (AMP) with and without hyaluronidase digestion, various silver stains, mainly the Wilder and Snook preparations for reticulin, and the Bodian stain for nerve fibers.

Follow-up information ranging from one month to 14 years was obtained in 46 cases. Autopsy material was studied in 20 of the 42 patients who died. Patients included in this study had either died or survived more than five years. All patients surviving less than five years were excluded.

The location, rate of mitotic activity, and size of the neoplasms were studied in relation to their biologic behavior. The rate of mitotic activity was expressed as the highest mitosis count, i.e., the highest number of mitotic figures present in 10 high-power ($\times 430$) fields (HPF) out of a sampling of 50 HPF, preferably 10 HPF in each of 5 different ares or sections of the tumor.

Results

Clinical Features

The age of the 46 patients at the time of diagnosis ranged from 10 to 71 years with 74% of the cases being evenly distributed between the ages of 20

Table 1. Age distribution of 46 cases of malignant schwannoma

Age/years	No. patients	%
0–9	–	–
10–19	8	17
20–29	12	26
30–39	12	26
40–49	5	11
50–59	5	11
60–69	3	7
70–79	1	2
80–89	–	–
Total	46	100

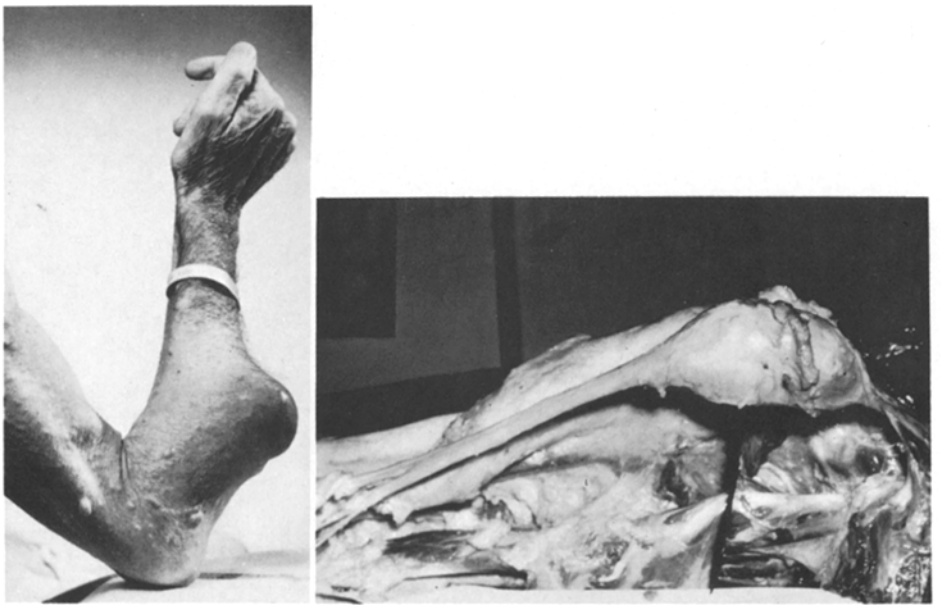


Fig. 1. Malignant schwannoma, right forearm in a 70-year-old man with neurofibromatosis. (AFIP Neg. No. 63–1655)

Fig. 2. Malignant schwannoma involving the left sciatic nerve of a 50-year-old man. The patient died of pulmonary metastasis 6 months after surgical removal of the tumor. (AFIP Neg. No. 57–1919)

Table 2. Anatomical distribution of 46 cases of malignant schwannoma

Anatomic location	No. patients	%
Head, neck	4	9
Trunk	17	37
Retroperitoneum	11	
Chest wall, back	6	
Upper extremities	7	15
Shoulder, axilla	4	
Forearm	2	
Upper arm	1	
Lower extremities	18	39
Thigh, knee	8	
Buttock, inguinal r.	7	
Lower leg	2	
Hip	1	
	46	100

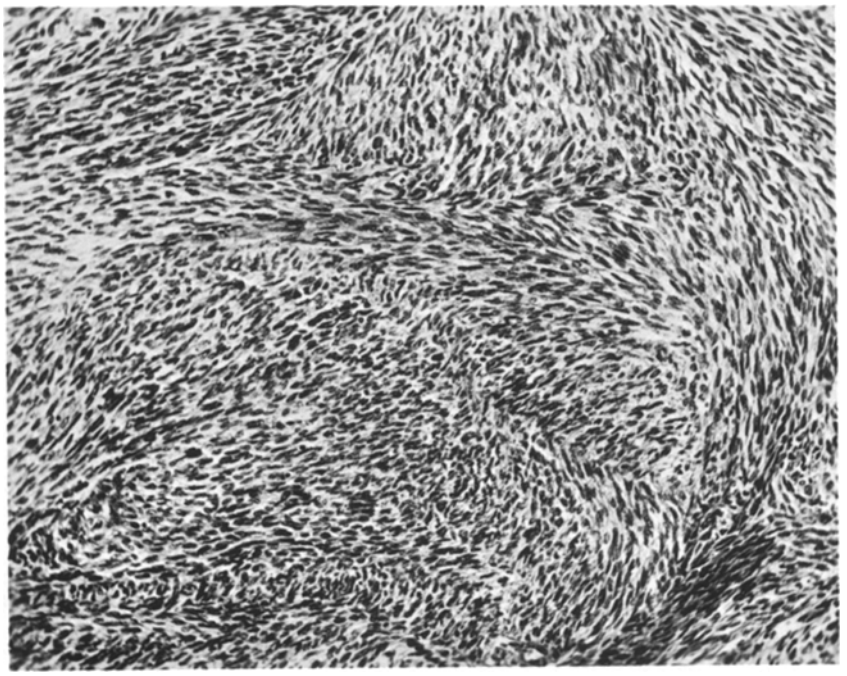


Fig. 3. Malignant schwannoma composed of well oriented, spindle shaped cells being arranged in ill-defined, sweeping fascicles. The tumor was removed from the retroperitoneum of a 33-year-old man. (AFIP Neg. No. 75-7172) ×130

and 50 years (Table 1). The mean age at the time of diagnosis was 32 years. There were 37 male patients and 9 female patients. There were 38 Caucasian patients, four Negro patients, and one Mongolian patient. Race was not stated for three patients.

In 43 cases the patients had multiple cutaneous neurofibromas. In the remaining three cases only a diagnosis of neurofibromatosis was given. In 16 cases the duration of neurofibromas was 3–36 years, the mean duration being 19 years. The neurofibromas had been present for "many years" in four additional patients and for "all their life" in five patients. A positive family history of neurofibromatosis was given in nine patients, denied in 21, and was unavailable in 16 patients. The most common presenting symptom of malignant schwannoma was a swelling or mass, occurring in 28 patients (Fig. 1). The mass was associated with pain in eight patients and had recently increased in size in three. In additional 12 patients pain was the presenting symptom. Five neoplasms in the retroperitoneum and three involving the sciatic nerve produced pain in the lower extremity. This pain was mostly of the sciatica type and in some cases was associated with motor weakness, hypesthesia, stiffness and tingling. One patient each presented with weakness and pain of the right arm, constipation and difficulty in urinating, and asthma related to partial respiratory obstruction by a tumor in the retropharynx. One neoplasm was detected by routine chest

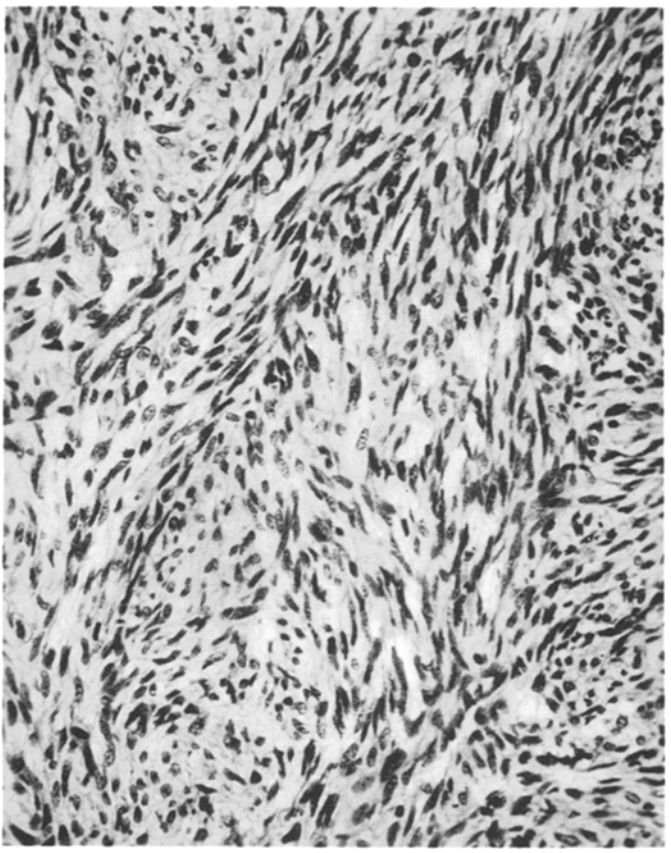


Fig. 4. Malignant schwannoma showing the striking contrast between the sharply defined, hyperchromatic nuclei and the pale staining, myxoid background. The tumor was removed from the right lumbar region of a 16-year-old boy with neurofibromatosis. (AFIP Neg. No. 79–10171) ×250

roentgenograms. Information regarding the presenting symptom was unavailable for two patients.

The duration of the presenting symptoms prior to diagnosis, given in 36 cases, ranged from 1 month to 2 years in 30 patients (median 6 months). In six patients the presenting symptoms had been present for $2\,^1/_2$ to 12 years (median $3\,^1/_2$ years).

Anatomic Location. Malignant schwannoma was most common in the lower extremities (18 cases) and in the retroperitoneum (11 cases). Next in frequency was the trunk (6 cases), followed by the upper extremities (7 cases) and the head and neck area (4 cases) (Table 2). Thirty-three of 46 tumors occurred near the central axis of the body (head and neck, trunk, retroperitoneum, and shoulder and pelvic girdles), whereas only 13 (28%) tumors occurred in the extremities proper (arm, forearm, thigh, and leg). Thirty-one of 46 neoplasms involved large peripheral nerves in these locations including eight that affected the sciatic

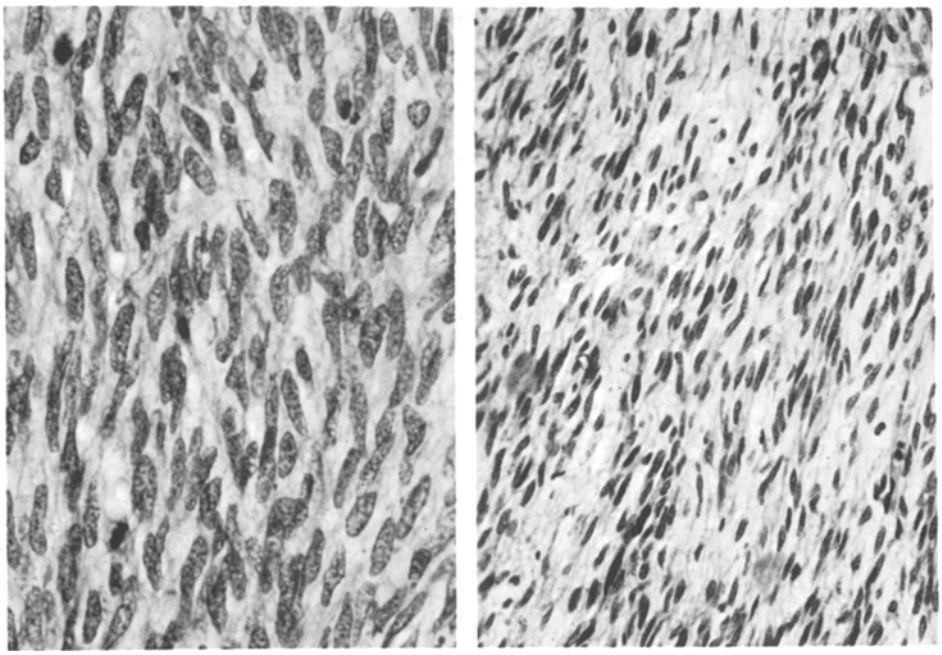


Fig. 5a and b. Cellular characteristics of malignant schwannoma, **a:** cells with hyperchromatic, wavy nuclei, and indistinct cytoplasm separated by small amounts of interstitial collagen and a myxoid matrix. (AFIP Neg. No. 79–10181) ×200. **b:** Plump, spindle cells with sharply defined nuclei showing an even chromatin pattern and absence of nucleoli. (AFIP Neg. No. 79–10189) ×350

nerve, four the popliteal, tibial or peroneal nerves, and three the cervical or brachial plexus.

Two patients had multiple malignant schwannomas. One of these developed a non-metastasizing malignant schwannoma of the right anterior chest three years before he died of a second malignant schwannoma of the right brachial plexus. The other patient had an intradural malignant schwannoma of the second sacral nerve one year prior to succumbing to a second malignant schwannoma of the sciatic nerve in the left buttock.

Pathological Features

Gross Observations. The size of the neoplasm, stated in 42 cases, ranged from 2.5 to 45 cm in greatest diameter, 79 percent being between 6 and 15 cm. The mean greatest dimension was 11 cm. The neoplasms were oval and sometimes pseudoencapsulated and in several cases formed a fusiform mass within a large nerve (Fig. 2). They were soft to firm in consistency and had a white to tan cut surface. Hemorrhage and necrosis were frequent findings.

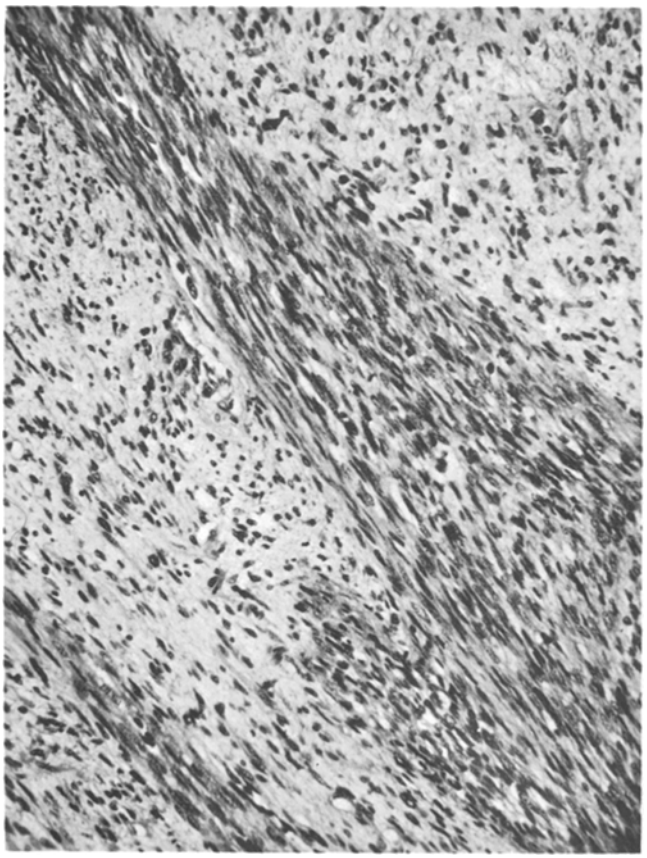


Fig. 6. Richly cellular fascicle of well oriented tumor cells traversing a less cellular, myxoid portion of a malignant schwannoma. (AFIP Neg. No. 79–10171) ×160

Microscopic Observations

As with the normal Schwann cell, the tumor cells had elongated, wavy or buckled, hyperchromatic nuclei that had a sharply outlined, or "punched-out" appearance and sparse cytoplasm with indistinct borders. Sometimes these cells were intermixed with cells having shorter and more rounded vesicular nuclei. Cellular pleomorphism or tumor giant cells were rare except in one case which resembled focally a malignant fibrous histiocytoma. Bodian preparations disclosed neurites in a few cases, most probably remnants of nerves entrapped by the expanding neoplasm.

The growth pattern varied considerably. Many of the tumors were extremely cellular and were composed of intersecting and swerving bundles of well oriented neoplastic cells and wavy collagen fibers forming a compact "herring-bone" pattern as in fibrosarcoma (Figs. 3, 4, and 5A and B). In others there were

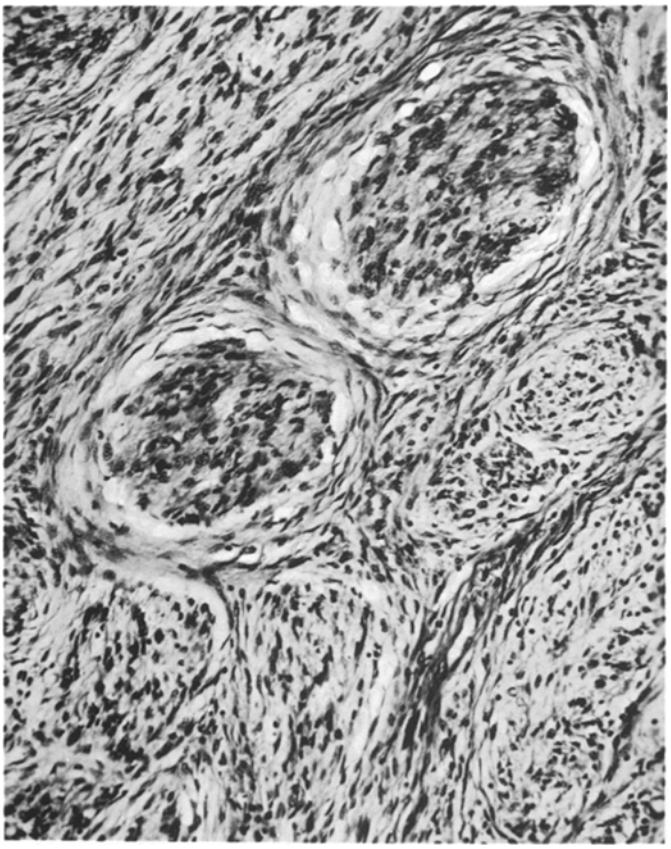


Fig. 7. Well defined bundles of tumor cells within a less cellular and more myxoid portion of a malignant schwannoma. (AFIP Neg. No. 77–2726) ×185

alternating cellular and less cellular, myxoid areas with loosely arranged tumor cells. In some of these tumors richly cellular bundles of fusiform cells traversed the myxoid areas, vaguely reminiscent of neural structures (Figs. 6, 7). In still other neoplasms the diffuse myxoid pattern predominated and was marked by the presence of large amounts of hyaluronidase-sensitive acid mucopolysaccharides (Fig. 8). In general, the stark contrast between the sharply outlined, "punched-out" hyperchromatic nuclei and the myxoid background greatly facilitated the diagnosis of malignant schwannoma (Figs. 4, 5, 6 and 8).

Another common characteristic of the tumor was its prominent vascular pattern. Often gaping, thin-walled blood vessels formed a pericytoma-like arrangement (Fig. 9) or blood vessels of smaller caliber were surrounded by a cuff of proliferated cells which, judging from their nuclear features and mitotic activity, constituted an inherent part of the neoplasm (Fig. 10). Growth within or along nerves was a common feature (Fig. 11). Surprisingly, palisaded nuclei were noted in only one of the neoplasms. In two tumors, however, the cells formed structures closely resembling Wagner-Meissner corpuscles. In two others

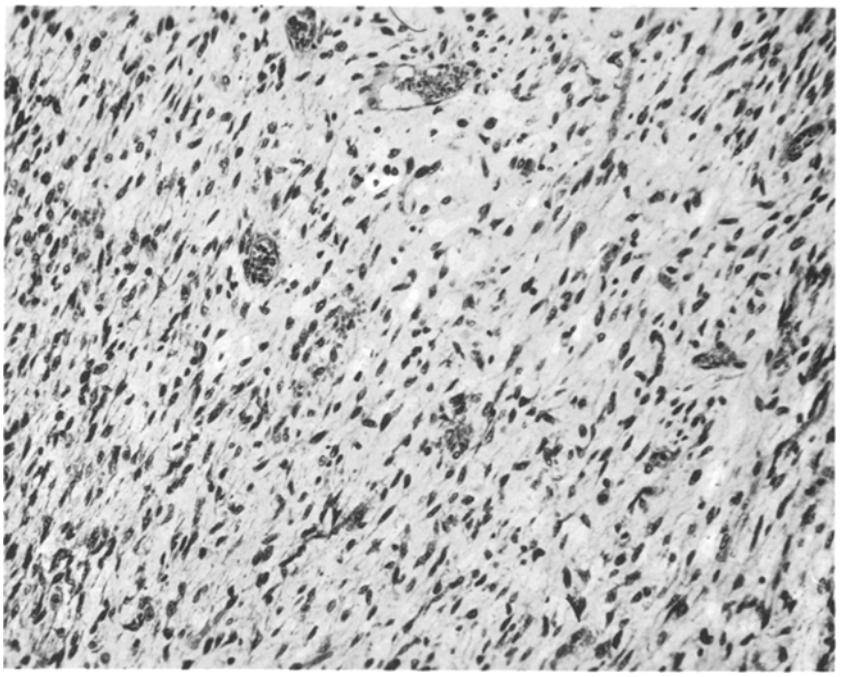


Fig. 8. Diffuse myxoid form of malignant schwannoma originating in the sacral plexus of a 22-year-old male. (AFIP Neg. No. 77–9744) ×160

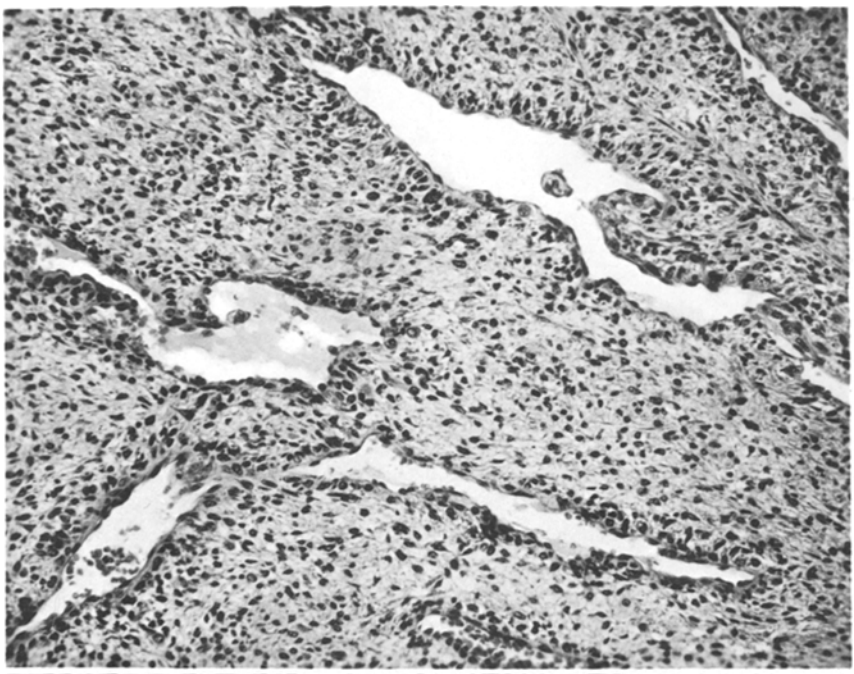
the cells were polygonal in shape and, as in an epithelial tumor, were arranged in cords and nests. Necrosis and hemorrhage were a prominent feature in the majority of cases.

Mesenchymal differentiation of the neoplastic cells occurred in both primary and recurrent malignant schwannomas. Rhabdomyoblasts, some with cross striations (malignant "Triton" tumor) were present in seven primary and one recurrent neoplasm (Figs. 12, 13), malignant cartilage in five (Fig. 14), and malignant bone in two tumors.

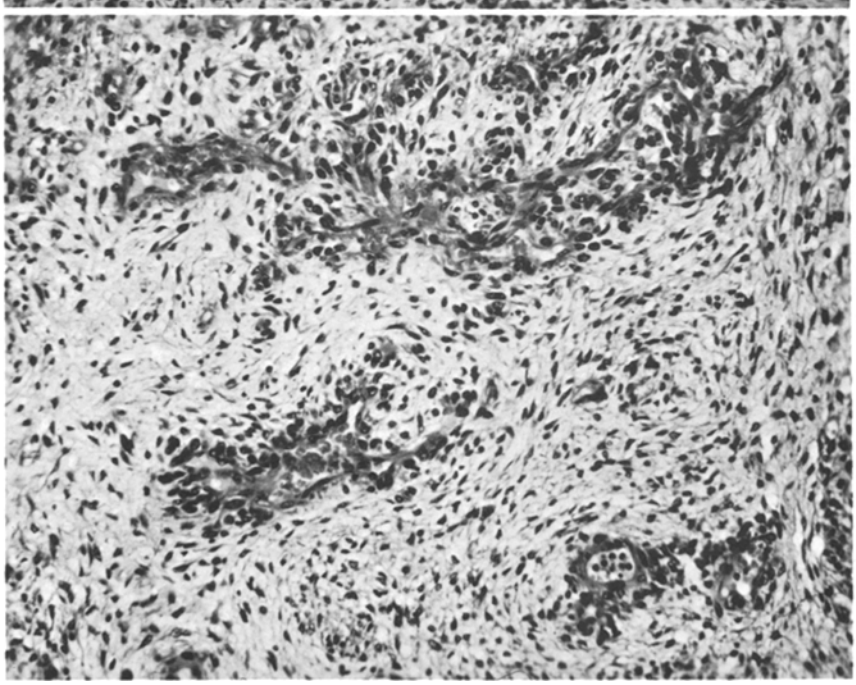
Of the 46 neoplasms twenty involved microscopically both a neurofibroma and a large nerve, 11 a neurofibroma, and 6 a large nerve. In nine cases no microscopic or clinical evidence as to any association with a neurofibroma or nerve was available.

Biologic Behavior and Results of Treatment

The majority of malignant schwannomas occurring in patients with neurofibromatosis pursued a highly malignant course. Thirty-two patients died of their tumors within two years following diagnosis. Seven additional patients died of their disease within three to five years and two within six to ten years. Only 4 of the 46 patients were alive and free of tumor at the end of the



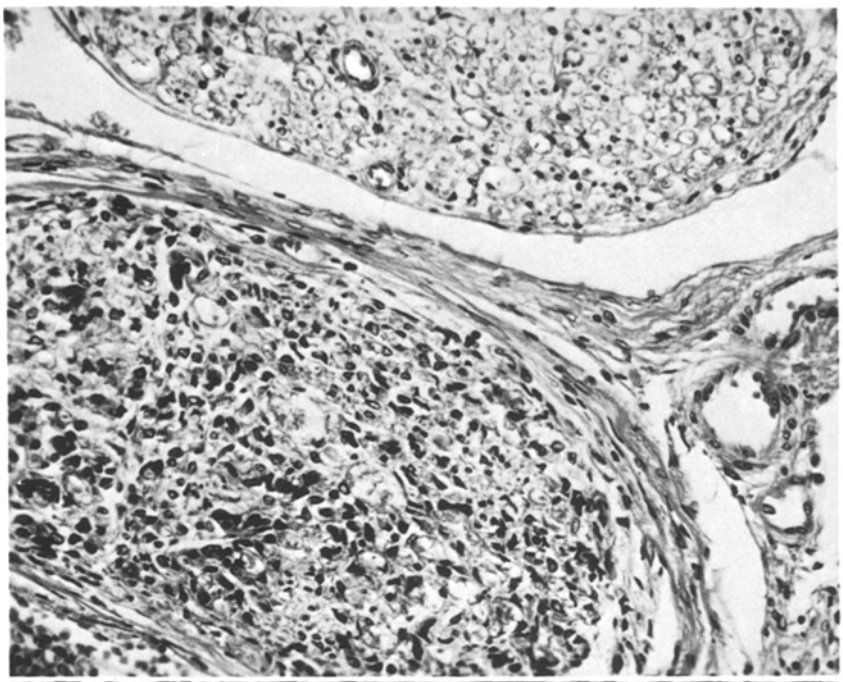
9



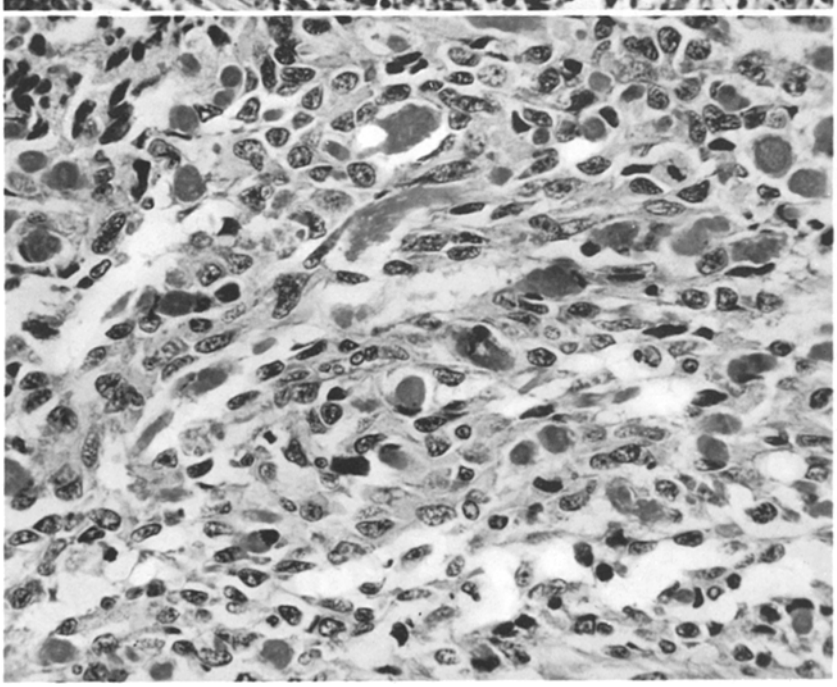
10

Fig. 9. Richly vascular, hemangiopericytoma-like pattern showing a slight increase in cellularity in close vicinity of the vascular spaces. (AFIP Neg. No. 79–10185) ×160

Fig. 10. Marked perivascular proliferation of neoplastic cells, a characteristic feature of many cases of malignant schwannoma. (AFIP Neg. No. 79–10173) ×100



11



12

Fig. 11. Malignant schwannoma involving and extending along the right femoral nerve of a 19-year-old man. (AFIP Neg. No. 79–10182) ×250

Fig. 12. Rhabdomyoblastic differentiation in a malignant schwannoma of the pelvis in a 63-year-old man. The patient had multiple neurofibromata in trunk and extremities. (AFIP Neg. No. 75–337) ×250

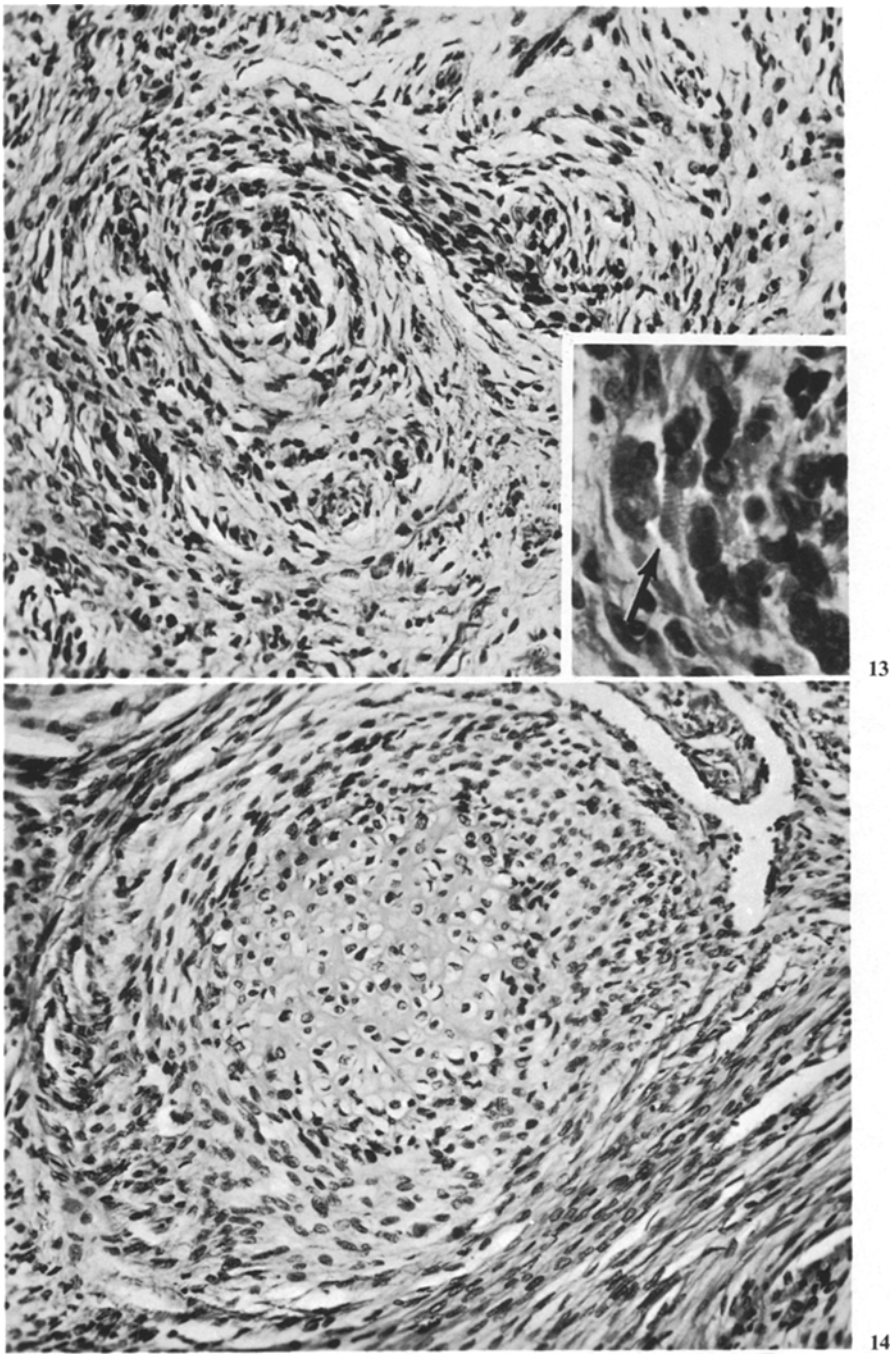


Fig. 13. Malignant schwannoma arising in a neurofibroma of the left gluteus in a 37-year-old man with focal rhabdomyoblastic differentiation (malignant "Triton" tumor). (AFIP Neg. No. 75–345) ×160. *Inset:* Rhabdomyoblasts with cross striations (*arrow*) from another portion of the tumor (AFIP Neg. No. 75–34) ×575

Fig. 14. Malignant cartilaginous metaplasia in a malignant schwannoma arising within the sciatic nerve of a 21-year-old male. Same case as Figure 7. (AFIP Neg. No. 78–1850) ×160

Table 3. Clinical course of malignant schwannoma

	No. of patients		%	
Alive:	*4*		8.7	
No recurrence or metastasis		1		2.2
Recurrence only		3		6.5
Metastasis		0		0
Dead:	*42*		91.3	
Recurrence only		12		26.1
Recurrence and metastasis		21		45.6
Metastasis only		8		17.4
Unrelated cause of death		1		2.2
Total	46		100	

follow-up period (5 to 15 years following diagnosis). A fifth tumor-free patient died of an unrelated disease (Table 3). Thus, the 5 year survival rate for patients having malignant schwannoma and neurofibromatosis was 15%.

Of the 41 lethal tumors, 12 recurred, 8 metastasized, and 21 recurred and metastasized. Five of the 12 tumors which recurred caused spinal cord compression which contributed to the patient's demise. In the majority of patients having metastatic disease, the metastatic tumors were distributed in a widespread fashion or were mainly in the lungs. Unusual sites of metastasis included: bone (8 tumors), lymph node (3 tumors), intestine (3 tumors), kidney (1 tumor), and adrenal gland (1 tumor).

In 41 patients who died of their tumors, 30 were treated by local excision and 11 by local excision followed by radical excision or amputation of the involved extremity. Palliative radiation therapy and chemotherapy using a wide variety of agents were given to 12 and 14 patients, respectively. Four of five patients who were tumor free at the end of the 5 to 15 year follow-up period were treated by local excision of the tumor. The fifth patient was treated by initial local excision of the tumor followed by amputation of the involved extremity.

The generally poor prognosis of the malignant schwannomas occurring in patients having von Recklinghausen's neurofibromatosis seemed to be best correlated with their occurrence near the central axis of the body, their high rate of mitotic activity (more than 6 mitotic figures/10 HPF), and their large size (more than 7 cm in greatest dimension). In contrast, the neoplasms which occurred in patients who were tumor free at the end of the 5 to 15 year follow-up period occurred in the peripheral extremities, tended to have a lower rate of mitotic activity, and tended to be smaller in size.

Thirty-two of the 41 lethal neoplasms occurred in locations near the central axis of the body whereas nine occurred in the extremities. All five of the tumors which occurred in patients who were tumor free at last follow-up occurred in the extremities. Thirty-two of 36 lethal tumors in which H & E slides of the primary tumor were available for study had a highest mitosis count of more than 6 mitotic figures/10 HPF and four tumors, 6 mitotic figures or less/

10 HPF. Two of three tumors which occurred in patients who were tumor free at last follow-up and in which H & E slides of the primary tumor were available for study had highest mitosis counts of 6 mitotic figures or less/10 HPF. The third tumor had 11 mitotic figures/10 HPF. Thirty of the 37 lethal tumors in which size data were available measured more than 7 cm in greatest dimension and the remaining seven tumors measured 7 cm or less. Three of five tumors which occurred in patients who were tumor free at last follow-up measured 7 cm or less in greatest dimension, and two tumors 10 and 12 cm.

Malignant schwannomas containing rhabdomyoblasts and malignant cartilage and bone did not differ from the other malignant schwannomas in their behavior.

Discussion

The tumor developed principally in patients between 20 and 50 years of age, usually having a long history of neurofibromatosis (median 19 years) marked by the presence of multiple neurofibromata and cafe au lait spots. Most of the neoplasms arose in a neurofibroma or a large nerve, especially in its more proximal portion. The sciatic nerve was most commonly involved.

The diagnosis of malignant schwannoma was based on the occurrence of malignant spindled cells closely resembling Schwann cells, the close association or origin of the malignant schwannoma in a neurofibroma, and the involvement of a nerve by the malignant schwannoma. The malignant, spindled cells were characterized by their elongated, wavy or buckled, hyperchromatic, sharply-outlined nuclei. Several additional histologic features were useful in making the diagnosis of malignant schwannoma. These included arrangement of the spindled tumor cells in a whorled pattern about thin-walled, gaping blood vessels, perivascular cellular proliferation, and the presence of a prominent myxoid stroma containing abundant, hyaluronidase-sensitive acid mucopolysaccharide. In the few cases in which these histologic features were sparse, the neoplasm closely resembled a fibrosarcoma. In these cases the diagnosis of malignant schwannoma was based largely on the close association of the neoplasm with a neurofibroma and/or nerve.

The malignant schwannoma also resembled other spindle cell sarcomas such as a leiomyosarcoma and synovial sarcoma. The leiomyosarcoma was characterized by more blunt-ended, oblong nuclei and more abundant and distinct cytoplasm containing longitudinal myofibrils that stained well with the Masson trichrome preparation. Although a poorly differentiated synovial sarcoma may closely resemble malignant schwannoma, including the presence of a pericytoma-like vascular pattern, the presence of a biphasic cellular pattern or focal calcification facilitate the diagnosis of synovial sarcoma. Cellularity and mitotic activity distinguish malignant schwannoma from neurofibroma.

The malignant schwannomas occurring in patients with neurofibromatosis frequently had a poor prognosis, 41 of 46 patients having died of their tumors, most with pulmonary metastasis. Lymph node metastasis was noted in only three cases. The five year survival rate was 15%. D'Agostino et al. (1963) and

Ghosh et al. (1973) have also noted the poor prognosis of this neoplasm. The exact explanation for this behavior is obscure. One contributing factor may be the location of the tumor. The lethal malignant schwannomas tended to occur in areas close to the central axis of the body where early detection was difficult. Thus the tumors tended to grow to a large size and metastasize before the diagnosis was made. In contrast, the tumors which occurred in patients who were tumor free at last follow-up involved the extremities where they were more amenable to early diagnosis and treatment. Another contributing factor may be higher degree of malignancy as reflected in the rate of mitotic activity. The lethal tumors tended to have higher rates of mitotic activity than neoplasms which occurred in patients who were tumor free at last follow-up.

Seven primary malignant schwannomas and one recurrent neoplasm in this study were malignant "Triton" tumors. Following the criteria established for malignant "Triton" tumor by Woodruff et al. (1973), these neoplasms had their origin in a nerve and/or occurred in patients with neurofibromatosis. They consisted mainly of spindled tumor cells closely resembling Schwann cells and contained bona fide neoplastic rhabdomyoblasts. These malignant "Triton" tumors and the malignant schwannomas which contained malignant cartilage and bone did not differ from the other malignant schwannomas in this series in their clinical presentation or behavior.

References

D'Agostino, A.N., Soule, E.H., Miller, R.H.: Primary malignant neoplasms of nerves (malignant neurilemomas) in patients without mainifestations of multiple neurofibromatosis (von Recklinghausen's Disease). Cancer **16**, 1003–1014 (1963)

D'Agostino, A.N., Soule, E.H., Miller, R.H.: Sarcomas of the peripheral nerves and somatic soft tissues associated with multiple neurofibromatosis (von Recklinghausen's disease). Cancer **16**, 1015–1027 (1963)

Ghosh, B.C., Ghosh, L., Huvos, A.G., Fortner, J.G.: Malignant schwannomas. A clinicopathologic study. Cancer **31**, 184–190 (1973)

Harkin, J.C., Reed, R.J.: Tumors of the peripheral nervous system. Atlas of tumor pathology, Second Series, Fascicle 3. Washington, D.C.: Armed Forces Institute of Pathology 1968

White, Jr., H.R.: Survival in malignant schwannoma. An 18-year study. Cancer **27**, 720–729 (1971)

Woodruff, F.M., Chernik, N.L., Smith, M.C., Millet, H.B., Foote, F.H.: Peripheral nerve tumors with rhabdomyosarcomatous differentiation (malignant "Triton" tumors). Cancer **32**, 426–439 (1973)

Received April 25, 1979