Spinal malignant nerve-sheath tumor or cellular schwannoma? A striking difference in prognosis

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Cellular schwannoma, a recently delineated entity, has a histological appearance mimicking that of malignant neoplasms. The aim of this study was to determine the outcome for patients treated for a spinal cellular schwannoma or malignant nerve-sheath tumor. A histological re-examination was conducted of 283 spinal tumors, considered to originate from a nerve root, that were treated in the Department of Neurosurgery between 1953 and 1985. After re-examination, 50 of these were determined to be other tumors or non-neoplastic lesions. The review yielded eight cellular schwannomas and six malignant nerve-sheath tumors out of 233 of nerve sheath origin. Immunohistochemical staining with a commercially available polyclonal antibody against S-100 protein was positive in all cases of cellular schwannoma, but negative for the malignant tumors. Clinical outcome was favorable for patients with cellular schwannomas, but uniformly poor for those with the malignant tumors.

Key Words: spinal tumor • cellular schwannoma • malignant nerve-sheath tumor • S-100 protein • prognosis

Malignant nerve-sheath tumors are rare and their true incidence is not known; however, a frequency of nerve-sheath tumors in the range of 2% to 13% has been described. An association with neurofibromatosis (NF) type 1 (NF1, von Recklinghausen’s disease) is seen in almost one-half of patients with malignant nerve-sheath tumors. Cellular schwannoma is a recently recognized subtype of schwannoma with a rather worrisome pseudosarcomatous histological appearance, but with a seemingly favorable clinical outcome. Tumors of nerve-sheath origin make up about one-fourth of spinal neoplasms. The benign nature of ordinary spinal schwannomas and neurofibromas has been established, but the outcome after surgical removal of spinal malignant nerve-sheath tumors and cellular schwannomas remains unsettled. The aim of this study was to establish the clinical behavior of these tumors. The entities of malignant schwannoma and neurofibrosarcoma are included in the term “malignant nerve-sheath tumor.”

Clinical Material and Methods

Patient Population

We retrieved the files of all patients treated for a spinal neoplasm at the Department of Neurosurgery, Helsinki University Central Hospital, between the years 1953 and 1985. After exclusion of patients diagnosed as having spinal meningioma, intramedullary glioma, ependymoma, spinal metastatic disease, or primary spinal bone tumor, there remained 296 patients with a spinal tumor suspected of originating from a nerve root. Pathological specimens from 283 of these patients were available for histological re-examination.

Information regarding the patients’ symptoms, signs, and radiological and operative findings was collected from the hospital records. Each patient’s present address or date of death was obtained from the Population Register Centre of Finland or the registers of local parishes. A copy of each death certificate was obtained from Statistics Finland. A detailed questionnaire on the present state of health was sent to all surviving patients. Follow-up evaluation until death or 1990 was complete.

Statistical calculations were made using the Medstat statistical computer package. The Mann-Whitney test was used for comparative statistics.

Histological and Immunohistochemical Studies

Re-examination of the paraffin sections, stained by the hematoxylin and eosin and van Gieson methods, was performed by a neuropathologist (M. J. J. H.), who was unaware of the clinical outcome of the patients. A

* Medstat statistical computer package obtained from Astra, Copenhagen, Denmark.
Malignant versus cellular spinal schwannoma

A semiquantitative grading system was used to assess mitotic activity, nuclear pleomorphism, cellularity, and the occurrence of necroses. Tumors showing increased cellularity or increased mitotic activity were stained using the immunoperoxidase method with polyclonal antibodies against S-100 protein, glial fibrillary acidic protein (GFAP), cytokeratin, and with monoclonal antibody against vimentin, desmin, epithelial membrane antigen, and leukocyte common antigen. Small pieces of the sarcomatous tumors were deparaffinized and processed for electron microscopic confirmation of the diagnosis using routine methods.

A tumor with the histological features of a schwannoma but displaying areas of increased cellularity, variable mitotic activity, some nuclear pleomorphism, and at least partial encapsulation was considered a cellular schwannoma. A tumor diagnosed as a malignant nerve-sheath tumor was characterized by high cellularity with spindle-shaped or polygonal cells, sometimes with considerable nuclear pleomorphism. The mitotic activity was high, and pathological mitotic figures were also seen. Malignant tumors showed infiltration of adjacent tissues. All tumors were associated with a nerve root. The histological differentiation between malignant nerve-sheath tumors and cellular schwannomas may sometimes be quite difficult, as illustrated by Fig. 1. The material contained eight cellular schwannomas, six malignant nerve-sheath tumors, 187 schwannomas, 32 neurofibromas, and 50 other tumors or non-neoplastic lesions, for a total of 233 tumors of nerve-sheath origin.

schwannoma or malignant nerve-sheath tumor are presented in Table 1. The age at diagnosis was significantly lower in patients with malignant nerve-sheath tumors (mean ± standard deviation, 27.7 ± 13.4 years) than in patients with cellular schwannomas (45.5 ± 14.6 years, p = 0.03). Both types of tumors occurred with equal frequency in both sexes. No patient with a cellular schwannoma showed any clinical signs of NF1 or NF2. Two patients with malignant tumors had clinical evidence of NF1 (Cases 9 and 11) and one was found to have bilateral acoustic neurinomas at autopsy (Case 12). One patient with a lumbar malignant nerve-sheath tumor (Case 9) had received radiotherapy for a Wilms' tumor 12 years earlier.

Clinical Presentation

The mean duration of symptoms was somewhat longer in patients with cellular schwannomas (25 months) than in patients with malignant nerve-sheath tumors (8.1 months), although the difference did not reach statistical significance (p = 0.14). The main presenting symptom in both patient groups was local or radiating pain, followed by progressing paraparesis. One patient with a cellular schwannoma (Case 2) and two with a malignant nerve-sheath tumor (Cases 9 and 10) were unable to walk at the time of operation. A very severe radiating pain was seen in one patient in the cellular-schwannoma group (Case 5) and two patients in the other group (Cases 11 and 13).

Radiography

Plain x-ray films of the spine were normal in four patients with cellular schwannomas and in three with malignant nerve-sheath tumors. Widening of an intervertebral foramen was revealed in two patients in both groups. Scalloping of the vertebral body was noted in one patient with a malignant tumor (Case 12), but destruction of bone was not observed in any case. Myelography showed an intradural extramedullary tu-

Patient Characteristics

The clinical data for patients with either cellular

\[ \text{S-100 protein and glial fibrillary acidic protein obtained from DAKO, Copenhagen, Denmark; cytokeratin obtained from Lab Systems, Espoo, Finland.} \]
malignant schwannoma in four patients with cellular schwannomas and in two with malignant nerve-sheath tumors. Total blockage was the myelographic finding in three patients in both groups. One patient with a malignant tumor (Case 11) underwent surgery without a myelography. At the time of diagnosing these tumors, magnetic resonance imaging was not available.

Operative Findings

At operation, six of the eight cellular schwannomas and three of the six malignant nerve-sheath tumors resembled benign schwannomas. One cellular schwannoma (Case 3) and two malignant nerve-sheath tumors (Cases 13 and 14) were unusually firm. In one patient in each group the tumor was softer and more bluish than a common schwannoma. In most cases the bleeding at operation or the surgeon’s impression of the tumor’s vascularity did not differ from that encountered at removal of benign schwannomas. Loss of blood exceeded 2000 ml in one patient with a cellular schwannoma (Case 7) and in two with malignant tumors (Cases 12 and 14). The extent of laminectomy ranged from one to five vertebral levels (median 2.4) in patients with cellular schwannomas and from one to three levels (median 2.2) in patients with malignant nerve-sheath tumors. Seven cellular schwannomas were intradural and one was totally extradural, growing into the brachial plexus. The cellular schwannomas were amenable to gross total removal with the exception of one tumor that was growing into the conus medullaris (Case 8). The malignant nerve-sheath tumors tended to grow both intra- and extradurally, but gross total removal was still achieved in four cases.

Immunohistochemical Findings

Immunohistochemical staining of the original pathological specimens could be performed on seven cellular schwannomas and four malignant nerve-sheath tumors. The immunohistochemical characteristics of these tumors are presented in Table 2. The tumor cells did not show any immunoreactivity when stained with monoclonal antibody against desmin, cytokeratin, epithelial membrane antigen, or leukocyte common antigen.

Patient Outcome

The clinical outcome was favorable in most patients with cellular schwannomas. One patient with a tumor growing into the conus medullaris (Case 8), despite partial removal and a wide decompressive laminectomy, developed total paraplegia and died 5 years later of acute myocardial infarction. In another patient (Case 7), deterioration of paraparesis led to the suspicion of tumor recurrence; reoperation 2 years after the original surgery yielded only scar tissue consistent with spinal arachnoiditis. The patient has since remained stable for 8 years. The other patients with cellular schwannomas have only minor sequelae. None of these patients received radiotherapy, although this treatment was discussed in at least two instances.

The clinical outcome for patients with malignant nerve-sheath tumors was very poor. The two patients with only partial removal of their tumor died within a few months with widespread metastatic disease. Even after a seemingly total removal followed by radiotherapy, local recurrence and metastases were the rule. The most common sites for metastatic spread were the lungs and liver, but cerebral metastases were also seen in one patient (Case 9). Case 14 deserves special attention. This woman developed symptomatic recurrence 2 years after the original gross total removal. She received radiotherapy and her paraparesis remained stable for 2 years. After renewed deterioration she underwent reoperation and the tumor was partially removed. She died 1 year after the second operation, with recurrent disease and pulmonary metastases.

The relative risk of death in patients with cellular schwannomas versus those with malignant nerve-sheath tumors is presented in Fig. 2.
Malignant versus cellular spinal schwannoma

TABLE 2

<table>
<thead>
<tr>
<th>Case No.</th>
<th>S-100</th>
<th>Vimentin</th>
<th>GFAP</th>
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<tr>
<td>cellular schwannoma</td>
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<tr>
<td>1</td>
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</tr>
<tr>
<td>8</td>
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<tr>
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<tr>
<td>9</td>
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* GFAP = glial fibrillary acidic protein; FP = faintly positive; --- = not available for re-examination and thus not studied.

Discussion

We are not aware of any previous reports on the incidence of spinal cellular schwannomas or malignant nerve-sheath tumors. The data for peripheral malignant nerve-sheath tumors vary widely. Ghosh, et al., found 115 malignant nerve-sheath tumors (12.7%) among 902 tumors of the peripheral nervous system. In contrast, Trojanowski, et al., reported a 2% incidence of malignant tumors in a series of 631 peripheral nerve-sheath tumors. Nittner found 35 tumors classified as sarcomas (not further specified) and 111 neurinomas in a series of 565 spinal tumors. Our series included six malignant nerve-sheath tumors among 233 spinal tumors of histologically proven Schwann cell origin, giving a rate of 2.6%.

The survival rates in published clinical series of peripheral malignant nerve-sheath tumors have been quite variable, with 5-year survival data in the range of 10% to 47%. This variation probably mostly reflects the difficulty of exact histological diagnosis. The outcome in our series of spinal malignant nerve-sheath tumors was very poor, despite surgery and radiotherapy. Valdueza, et al., have reported a somewhat more favorable outcome in their series of five spinal malignant schwannomas. The observed difference in outcome may be due to their short follow-up period and differences in the histological criteria for malignancy.

A wide local excision of the tumor is hardly ever possible in the narrow spinal canal, which diminishes the chance for cure. Furthermore, the rich vascular supply of the spinal canal increases the risk of hematogenous spread. One of our patients also had cerebral metastases from a malignant nerve-sheath tumor. This site for metastatic spread has been reported only twice before.

In the earlier literature, the two types of NF (NF1 and NF2) were not clearly separated. About one-half of peripheral malignant nerve-sheath tumors occur in patients with NF. These patients tend to be younger and their prognosis is poorer than for non-NF patients (solitary malignant nerve-sheath tumors). Our series included two patients with a clinical diagnosis of NF1 and one patient who was found to have bilateral acoustic schwannomas at autopsy, consistent with a diagnosis of NF2, indicating that malignant nerve-sheath tumors may occur in association with both types of NF.

Cellular schwannoma was described by Woolliff, et al., in 1981. The tumor is characterized by high cellularity, moderate nuclear atypia, and moderate mitotic activity, but no Verocay bodies. Altogether, 104 patients with this type of tumor have been reported by Fletcher, et al., Lodding, et al., and White, et al. Most of the tumors were located retroperitoneally or mediastinally; three tumors had extension into the spinal canal and two were located intracranially on the acoustic nerve. The outcome was favorable, with only four local recurrences and no metastatic spread. The clinical behavior of spinal cellular schwannoma seems as benign as that of cellular schwannoma in other locations. The only recurrence was seen in a patient with a partial removal of the tumor. Four patients with cellular schwannoma in association with NF1 have been described. None of our patients had any clinical signs of either type of NF. Fletcher, et al., found 18 cellular schwannomas among 635 tumors of peripheral nerves, giving a rate of 2.8%. In our series, eight cellular schwannomas made up 3.4% of the 233 spinal tumors considered to originate from a nerve root.

Staining with polyclonal antibodies against the S-100 protein is a widely used immunohistochemical method for the identification of tumor originating from Schwann cells and melanocytes. Malignant nerve-sheath tumors show variable staining patterns for S-100 protein. Hayashi, et al., showed that malignant nerve-sheath tumors stain with antibodies against the S-100 a subunit but not the antibodies against the S-100 B subunit. Most cellular schwannomas show strong immunoreactivity against S-100 protein. In our material all cellular schwannomas showed positive immunoreactivity for S-100 protein. No immunoreactivity for S-100 protein was found in any of the four malig-
nant tumors that were available for immunostaining using a polyclonal antibody against both α and β sub-
units. The lack of immunoreactivity probably reflects the low degree of differentiation in these tumors, cor-
responding to the poor clinical outcome. The consistent immunoreactivity for GFAP observed by Lodding, et al., 13 in cellular schwannomas could not be confirmed in our series.

We conclude that spinal cellular schwannomas are benign lesions, despite their histological appearance, and are curable with total removal. Radiotherapy is not indicated. Spinal malignant nerve-sheath tumors, on the other hand, are associated with a very poor prognosis. A correct histological diagnosis is therefore of utmost importance.

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