Case Report

Primary malignant peripheral nerve sheath tumor of the cauda equina in a child case report

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Study design: A case report of primary malignant peripheral nerve sheath tumor (MPNST) of the cauda equina in a child is presented, and the literature is reviewed.

Objective: To discuss the problems involved in the treatment of primary intradural MPNSTs.

Setting: A department of orthopaedic surgery in Japan.

Methods: A 4-year-old boy complained of low-back pain radiating to the left calf. MRI revealed an intradural tumor at L3–L5 level. Following laminectomy of L3, L4 and L5, the tumor was removed *en bloc*. Based on pathological and immunohistological findings, the tumor was diagnosed as an MPNST.

Results: Although adjuvant chemotherapy was administered local recurrence and cerebral and spinal metastases of the tumor were found 6 months after the operation. Following additional incomplete removal of the recurrent tumor, radiation therapy was administered. Although recurrent and metastatic tumors disappeared or diminished in size by radiation, tumors increased in size thereafter, despite additional adjuvant chemotherapy. At 21 months after the first operation, he died of pneumonia.

Conclusions: Reported clinical outcomes for patients with primary intradural MPNST are very poor. Although no gold standard for the treatment of tumors has been established yet, surgical removal of tumors combined with postoperative high-dose radiation may be recommended.

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Introduction

Malignant peripheral nerve sheath tumor (MPNST) is a spindle-shaped cell sarcoma originating from Schwann cells, fibroblastic cells or perineural cells in peripheral nerves¹ and tends to occur in the subcutaneous soft tissues and muscles in the extremities and trunk. This tumor is frequently complicated by neurofibromatosis type I, von Recklinghausen disease.^{2–9} The tumors are usually developed from the sciatic nerve, brachial plexus and sacral plexus. Although large MPNSTs of the thoracic or abdominal cavity may sometimes exhibit secondary spinal involvement,¹⁰ primary intradural MPNSTs are very rare^{11–14} and have never noted in a child without neurofibromatosis. In this report, we present a case of primary MPNST of the cauda equina in a child without evidence of neurofibromatosis on physical examination who was treated by

surgery, chemotherapy and radiation therapy and discuss the problems involved in the treatment of this tumor.

Case

A 4-year-old boy was admitted to our hospital complaining of severe low-back pain and calf pain on the left side. On admission, urinary dysfunction was observed. The patellar and Achilles tendon reflexes were diminished bilaterally. Neither sensory abnormality nor muscle weakness was noted in his upper or lower extremities. No cranial nerve palsy, convulsions or clouding of consciousness was observed. There were no superficial stigmata of neurofibromatosis, including café-au-lait spots or terminal nerve twigs. Laboratory data were within normal limits. He had no previous medical history or family history of neoplastic disease or neurofibromatosis.

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Neither radiographic nor CT examinations revealed distinct abnormalities, such as kyphoscoliosis, vertebral scalloping, widening of neural foramina or the spinal canal or erosion of pedicles, in the lumbar spine. MRI revealed a tumor with nonuniform isointense signal on T1-weighted and T2-weighted images in the lumbar spinal canal from L3 to L5. Gadolinium-enhanced MRI revealed enhancement of the tumor except in multiple foci of high intensity (Figure 1).

Total removal of the tumor was performed. Following laminectomy of L3, L4 and L5, a longitudinal incision was made on the center of the exposed dura. A dark-red soft tumor, 6 cm in length and 1.5 cm in diameter, protruded over the entire area. The cauda roots were severely compressed by the tumor. Following resection of the cauda root with a distinct connection to the tumor, the tumor was gently detached from adherent cauda roots using a spatula and then removed *en bloc*. After surgery, low-back pain and calf pain disappeared and urinary dysfunction was improved.

On microscopic examination, the tumor exhibited hypercellularity and increased mitotic activity. A large number of spindle-shaped cells having a high nuclear-to-cytoplasmic ratio were arranged in short and long fascicles (Figure 2). A small number of round- and oval-shaped cells were diffusely observed. Immunohistologically, the tumor cells were strongly positive for vimentin staining and positive for α -smooth muscle actin (SMA). Few cells were positive for S-100 protein. Based on these pathological and immunohistological findings, the tumor was diagnosed as an MPNST.

The patient received intravenous chemotherapy after the operation. The protocol consisted of six cycles of intensive multiagent chemotherapy with use of vincristine sulfate (1.5 mg/m^2 of skin in dose per one cycle), cyclophosphamide (600 mg/m^2 of skin in dose per one cycle), and pirarubicin hydrochloride (30 mg/m^2 of skin in dose per one cycle). Recurrence of the tumor was not

found on MRI examinations performed until 4 months after the operation.

At 6 months after the operation, however, enhanced masses were observed in the lumbar dural tube on enhanced MRI, and the patient began to complain of low-back pain radiating to the left calf, muscle weakness in both lower extremities and urinary dysfunction again. Removal of the recurrent tumor was attempted. However, the conus medullaris and most of the caudal roots could not be separated from the tumor mass, since the tumor was severely adherent to them. Thus, partial removal of the tumor was performed. The tumor exhibited exactly the same histopathological features as described above.

At 1 month after the second operation, MRI revealed an enlarging recurrent tumor in the lumbar spine and

Figure 2 Histological findings. The tumor exhibited hypercellularity and increased mitotic activity. A large number of spindle-shaped cells having a high nuclear-to-cytoplasmic ratio were arranged in short and long fascicles

Figure 1 MRI of lumbar spine before the first operation: (a) T1-weighted sagittal view, (b) T2-weighted sagittal view and (c) enhanced MRI sagittal view. MRI revealed a tumor of nonuniform isointense signal on T1-weighted and T2-weighted images in the lumbar spinal canal from L3 to L5. Gadolinium-enhanced MRI revealed enhancement of the tumor except in the multiple foci of high intensity

metastatic tumors in the brain and thoracic spine (Figure 3). External-beam radiation was administered to the brain, thoracic spine and lumbar spine. The total dose was 36 Gy in the brain, 30 Gy in the thoracic spine and 40 Gy in the lumbar spine. After the radiation therapy, tumors disappeared in the thoracic spine and diminished in size in brain and lumbar spine (Figure 4).

Figure 3 Enhanced MRI after the second operation: (a) sagittal view of brain, (b) sagittal view of cervicothoracic spine and (c) sagittal view of lumbar spine. At 1 month after the second operation, MRI revealed an enlarging recurrent tumor in the lumbar spine and metastatic tumors (arrow) in the brain and upper thoracic spine

Figure 4 Enhanced MRI after the radiation therapy: (a) sagittal view of brain, (b) sagittal view of cervicothoracic spine and (c) sagittal view of lumbar spine. After the radiation therapy, tumors disappeared in the upper thoracic spine and diminished in size in brain (arrow) and lumbar spine

Low-back pain and calf pain were improved. However, muscle weakness in both lower extremities and urinary dysfunction were not improved. Three additional cycles of chemotherapy with use of vinblastine sulfate (4 mg/m² of skin in dose per one cycle), actinomycin-D (1 mg/m² of skin in one cycle), cyclophosphamide (600 mg/m² of skin in dose per one cycle), bleomycin hydrochloride (20 mg/m² of skin in dose per one cycle), and cisplatin (120 mg/m² of skin in dose per one cycle) were administered. No lung or liver metastasis was observed on CT examination. However, cerebral and lumbar spinal tumors increased in size gradually. He died of pneumonia 21 months after the first operation.

Discussion

MPNSTs account for 5% of malignant soft-tissue tumors in the extremities and trunk, and have an estimated incidence of 0.001% in the general population.^{4,15} The mean age of patients with tumors at diagnosis was 31.6 years as reported by Kourea *et al*,¹⁰ 34.0 years as reported by Ducatman *et al*,⁴ and 37.4 years as reported by Wanebo *et al*.¹⁶ Reports of these tumors in children are rare.^{17–20} MPNSTs located in the extremities and trunk are usually high-grade and clinically aggressive, and the prognosis of patients with them is poor. Wanebo *et al*¹⁶ reported that the Kaplan–Meier survival rate was 62% at 3 years and 43.7% at 5 years. Sordillo *et al*²¹ reported that the 5-year survival rate for patients with von Recklinghausen's disease was 23% compared with 47% for patients without von Recklinghausen's disease. Kourea *et al*¹⁰ reported that 80% of patients with tumors in the subdiaphragmatic and intrathoracic spaces died, with mean survival of 8.5 months and 2-year and 5-year survival rates of 35 and 16%. For children, Meis *et al*¹⁷ reported a median survival of 45 months.

Although primary MPNSTs of the spinal canal are extremely rare, reported clinical outcomes for patients with them are very poor.^{11–14} Seppala and Haltia¹¹ reported that five patients with primary intradural MPNST died between 2 months and 6 years after surgery with widespread metastatic disease. They noted that local recurrence and metastases were the rule even after seemingly total removal. Thomeer *et al*¹² also noted that apparent radical surgery of these tumors yielded disappointing results. On the other hand, Acharya *et al*¹⁴ reported that a patient with MPNST in the cauda equina attained significant recovery after 18 months of surgery. Valdueza *et al*¹³ also reported that two of three patients with complete removal of their tumor were alive with free of disease. However, their follow-up period was short, 7 months in one patient and 8 months in the other. The reported cases with primary intradural MPNST are summarized in Table 1. In the present patient, surgical *en bloc* resection of the tumor was performed. However, local recurrence and intradural metastases of the tumor was found postoperatively. In the narrow spinal canal, radical excision of tumor with a margin of normal tissue is hardly ever

Table 1 Previous reported cases of primary intradural malignant peripheral sheath tumor

Case no.	Authors	Age (years)/gender	Level of tumor	Tumor removal	Local recurrence	Metastases	Outcome
1	Thomeer <i>et al</i>	42/M	L	Com	Yes	No	Alive with disease, 3 yrs
2	Valdueva <i>et al</i>	43/F	T	Inc	Yes	No	Alive with disease, 10 yrs
3		47/M	C	Com	Yes	?	Dead, 18 mos
4		18/M	C	Com	No	No	Free of disease, 8 mos
5		70/F	C	Com	No	No	Free of disease, 7 mos
6	Seppala <i>et al</i>	13/M	L	Inc	Yes	Yes	Dead, 2 mos
						(intradural metastases)	
7		13/M	L	Com	Yes	Yes	Dead, 7 mos
8		35/M	L	Com	Yes	Yes	Dead, 18 mos
9		23/F	T	Com	Yes	Yes	Dead, 8 mos
10		37/F	C	Com	Yes	Yes	Dead, 6 yrs
11	Acharya <i>et al</i>	32/M	L	Com	No	No	Free of disease, 18 mos
12	Current study	4/M	L	Com	Yes	Yes	Dead, 21 mos
						(intradural metastases)	

M = male; F = female; C = cervical spine; T = thoracic spine; L = lumbar spine; Com = complete removal, Inc = incomplete removal; yrs = years; mos = months

possible without causing neurological injury. Insufficient removal of tumor and spillage of highly malignant cells may be the cause of recurrence and metastases.

In general, adjuvant radiation therapy has been believed not to significantly alter the survival of patients with MPNSTs located in the trunk and extremities.^{6,17,22} Recently, however, the role of radiation therapy in treatment of peripheral MPNST has been expanding, and many authors support the use of adjuvant radiation therapy even with clear surgical margins.^{5,18,23–27} Efficacy of radiation therapy for the treatment of primary intraspinal MPNSTs was reported by Valdueva *et al*,¹³ who noted that decompression combined with postoperative high-dose radiation appeared to be the best therapy in patients who could not undergo radical tumor excision. They reported two patients who underwent incomplete surgical removal of tumors followed by local radiation. One of them was alive with disease 4 years after surgery and the other was alive with disease 10 years after surgery. They also noted that radiation should be administered after local recurrence. Acharya *et al*¹⁴ also described that postoperative radiotherapy might help eradicate or suppress the residual tumor growth. However, the outcomes in other series with use of radiation therapy after surgical removal of tumors were poor.^{11,12} The observed difference in efficacy of radiation therapy may be due to differences in histological grade of malignancy. It was reported that lack of immunoreactivity against S-100 protein probably reflects low degree of differentiation in these tumors, corresponding to poor clinical outcome.¹¹ In the present patient, few tumor cells exhibited positive immunoreactivity for S-100 protein. Thus, although recurrent and metastatic tumors disappeared or diminished in size by radiation, tumors increased in size thereafter, despite additional adjuvant chemotherapy. For tumors with a low grade of malignancy, however, adjuvant radiation therapy may be useful. Following surgical removal of tumors, therefore, high-dose radiation may be admini-

strated to patients with these tumors. To avoid radiation myelopathy, however, no more than 50 Gy in total dose should be administered at each level.

For patients with MPNSTs located in the extremities and trunk, it was reported that adjuvant chemotherapy has not convincingly been proven to be successful^{4,17,21} and should be limited to desperate cases of disseminated metastatic disease.^{27–29} However, no investigator has reported the role of adjuvant chemotherapy in treatment of primary intradural MPNST. It was reported that the most common sites for metastatic spread after removal of intradural MPNSTs were the lungs and liver in patients not treated by chemotherapy.¹¹ Although the role of chemotherapy is unclear, no lung or liver metastasis was observed in our patient after chemotherapy. However, local recurrence and intradural metastasis could not be avoided and were not improved with the use of various antineoplastic agents despite their penetrating into cerebrospinal fluid. Therefore, it remains unclear whether adjuvant chemotherapy following surgical removal should be performed for the treatment of primary intradural MPNST.

In conclusion, we treated a child with primary MPNST of the cauda equina by surgery, radiation and adjuvant chemotherapy and obtained a disappointing result. Although no gold standard for the treatment of primary intradural MPNST has been established yet, surgical removal of tumors combined with postoperative high-dose radiation may be recommended.

References

- Hirose T *et al*. Malignant peripheral sheath tumor (MPNST) showing perineural cell differentiation. *Am J Surg Pathol* 1989; **13**: 613–620.
- D'Agostino AN, Soule EH, Miller RH. Primary malignant neoplasms of nerves (malignant neurilemmomas) in patients without manifestations of multiple neurofibromatosis (von Recklinghausen's disease). *Cancer* 1963; **16**: 1003–1013.

- 3 Dasgupta TK, Brasfield RD. Solitary malignant schwannoma. *Ann Surg* 1970; **171**: 419–428.
- 4 Ducatman BS, Scheithauer BW, Piepgras DG, Reiman HM, Ilstrup M. Malignant peripheral nerve sheath tumors. A clinicopathologic study of 120 cases. *Cancer* 1986; **57**: 2006–2021.
- 5 Nambisan RN, Rao U, Moore R, Karakousis CP. Malignant soft tissue tumors of nerve sheath origin. *J Surg Oncol* 1984; **25**: 268–272.
- 6 Riccardi VM, Powell PP. Neurofibrosarcoma as a complication of von recklinghausen neurofibromatosis. *Neurofibromatosis* 1989; **2**: 152–165.
- 7 Sorenson SA, Mulvihill JJ, Nielson A. Long-term follow-up of von Recklinghausen neurofibromatosis. *N Engl J Med* 1986; **314**: 1010–1015.
- 8 Kett-White R, Martin JL, Jones EW, O'Brien C. Malignant spinal neurofibrosarcoma. *Spine* 2000; **25**: 752–755.
- 9 Evans DG, Baser ME, McGaughan J, Sharif S, Howard E, Moran A. Malignant peripheral nerve sheath tumors in neurofibromatosis 1. *J Med Genet* 2002; **39**: 311–314.
- 10 Kourea HP, Bilsky MH, Leung DHY, Lewis JJ, Woodruff JM. Subdiaphragmatic and intrathoracic paraspinal malignant peripheral nerve sheath tumors. A clinicopathologic study of 25 patients and 26 tumors. *Cancer* 1998; **82**: 2191–2203.
- 11 Seppala MT, Haltia MJ. Spinal malignant nerve-sheath tumor or cellular schwannoma? A striking difference in prognosis. *J Neurosurg* 1993; **79**: 528–532.
- 12 Thomeer RTWN, Bots GTAM, von Dulken H, Luyendijk W, Helle P. Neurofibrosarcoma of the cauda equina. Case report. *J Neurosurg* 1981; **54**: 409–411.
- 13 Valdueza JM, Hagel C, Westphal M, Hansel M, Herrmann H. Primary spinal malignant schwannoma: clinical, histological and cytogenetic findings. *Neurosurg Rev* 1991; **14**: 283–291.
- 14 Acharya R, Bhalla S, Sehgal AD. Malignant peripheral nerve sheath tumor of the cauda equina. *Neurol Sci* 2001; **22**: 267–270.
- 15 Lewis JJ, Brenna MF. Soft tissue sarcomas. *Curr Probl Surg* 1996; **33**: 817–880.
- 16 Wanebo JE, Malik JM, VandenBerg SR, Wanebo HJ, Driesen N, Persing JA. Malignant peripheral nerve sheath tumors. A clinicopathologic study of cases. *Cancer* 1993; **71**: 1245–1253.
- 17 Meis JM, Enzinger FM, Martz KL, Neal JA. Malignant peripheral nerve sheath tumors (malignant schwannoma) in children. *Am J Surg Pathol* 1992; **16**: 694–707.
- 18 Raney B, Schnauffer L, Ziegler M, Chatten J, Littman P, Jarrett P. Treatment of children with neurogenic sarcoma: experience at Children's Hospital of Philadelphia. *Cancer* 1987; **59**: 1–5.
- 19 Komori M, Yabuuchi H, Kuroiwa T, Nagatoshi Y, Ichinose Y, Hachitanda Y. Thoracic malignant peripheral nerve sheath tumour mimicking a pleural tumour: a rare pedunculated appearance. *Pediatr Radiol* 2003; **33**: 578–581.
- 20 Oguzkurt P, Kayaselcuk F, Arda IS, Barutcu O, Tuncer I, Oz S. Anterior abdominal wall malignant peripheral nerve sheath tumor in an infant. *J Pediatr Surg* 2001; **36**: 1866–1868.
- 21 Sordillo PP *et al*. Malignant schwannoma – clinical characteristics, survival, and response to therapy. *Cancer* 1981; **47**: 2503–2509.
- 22 Ariel IM. Tumors of the peripheral nervous system. *Semin Surg Oncol* 1988; **4**: 7–12.
- 23 Basso-Ricci S. Therapy of malignant schwannomas: usefulness of an integrated radiologic surgical therapy. *J Neurosurg Sci* 1989; **33**: 253–257.
- 24 Hruban RH, Shiu MH, Senie RT, Woodruff JM. Malignant peripheral sheath tumors of the buttock and lower extremity: a study of 43 cases. *Cancer* 1990; **66**: 1253–1265.
- 25 Karakousis CP, Velez AF, Emrich LJ. Management of retroperitoneal sarcomas and patient survival. *Am J Surg* 1985; **150**: 376–380.
- 26 Lindberg RD, Martin RG, Romsdahl MM, Barkley Jr HT. Conservative surgery and postoperative radiotherapy in 300 adults with soft tissue sarcomas. *Cancer* 1981; **47**: 2391–2397.
- 27 Storm FK, Eilber FR, Mirra J, Morton DL. Neurofibrosarcoma. *Cancer* 1980; **45**: 126–129.
- 28 Goldman RL, Jones SE, Heusinkveld RS. Combination chemotherapy of metastatic malignant schwannoma with vincristine, adriamycin, cyclophosphamide, and imidazole carboxamide: a case report. *Cancer* 1977; **39**: 1955–1958.
- 29 Pinedo HM, Kenis Y. Chemotherapy of advanced soft-tissue sarcoma in adults. *Cancer Treat Rev* 1977; **4**: 67–86.