Primary pediatric intraspinal sarcomas

Report of 3 cases

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Sarcomas that arise from within the spinal canal are rare, particularly within the pediatric population. In general, these primary intraspinal sarcomas are highly aggressive, posing unique treatment challenges with respect to surgery and choice of adjuvant therapy. The goal must be to obtain the most complete resection possible to minimize the risk of recurrence and metastasis, while preventing potential neurological deficits that may result from aggressive surgery.

Among these primary intraspinal sarcomas are malignant peripheral nerve sheath tumors and members of the Ewing sarcoma family of tumors. The authors present 3 cases of unique spinal sarcomas in children—2 malignant peripheral nerve sheath tumors in patients without neurofibromatosis and an intradural extraskeletal Ewing sarcoma arising from the sensory component of a lumbar spinal nerve—and discuss their management and outcome with a review of the current literature. (DOI: 10.3171/2009.3.PEDS08272)

Key Words • pediatric tumor • spine • sarcoma • Ewing sarcoma malignant peripheral nerve sheath tumor

Abbreviations used in this paper: EES = extraskeletal Ewing sarcoma; ESFT = Ewing sarcoma family of tumors; MPNST = malignant peripheral nerve sheath tumor; NF1 = neurofibromatosis Type 1.
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and only 30% of patients are disease free at 5 years after diagnosis.3,48 Malignant peripheral nerve sheath tumors typically arise along a peripheral nerve and can extend into the intraspinal compartment by tracking along the nerve through the neural foramen. Although they are extremely rare, primary intraspinal MPNSTs have been reported in a small number of cases.1,5,71,78,87

The ESFTs are a group of small, round-cell neoplasms of neuroectodermal origin that arise principally in children and young adults. These lesions comprise roughly 3% of all pediatric malignancies.67 Ninety percent of such cases present in the first and second decades of life, with a peak incidence between 5 and 13 years of age. Ewing sarcoma is the most common malignant spinal bone tumor in children, presenting as a primary spine tumor in 3.5%.24,34,85 Like MPNSTs, these sarcomas can secondarily invade the spine or arise from the spine itself. Ewing sarcomas are aggressive lesions, with ~25% of patients having metastatic disease at the time of diagnosis.57 Despite aggressive treatment, 30–40% of patients with localized disease and 80% of patients with metastatic disease die of disease progression.68

For both of these forms of sarcoma, resection is an important component of treatment. Retrospective evidence suggests that resection of both ESFTs9,14,25,54,68,69,75 and MPNSTs13,29 results in higher rates of local tumor control and patient survival. The goal of surgery in these lesions is to perform an en bloc resection, if possible, with negative margins, although that is clearly influenced by the location and extent of tumor growth. Adjuvant or neoadjuvant chemotherapy and radiation therapy are often included in the treatment strategy.54,59 Because of the rarity of these lesions, prospective randomized trials assessing the efficacy of adjuvant therapies have not been feasible, and the use of these therapies is frequently determined on an individualized basis. We present 3 cases of primary intraspinal sarcoma in children, and discuss their management.

Case Reports

Case 1

History and Examination. This 8-month-old boy presented with a 1-week history of left arm weakness and overall decreased motor activity. The clinical presentation suggested that he had a brachial plexopathy, and this was investigated with electromyography and nerve conduction studies. On examination, he had right upper- and bilateral lower-extremity hyperreflexia with diffuse left upper-extremity weakness and absence of left brachioradialis and biceps reflexes. There was no history of neurocutaneous syndromes, and the remainder of the examination was noncontributory.

Magnetic resonance imaging revealed a large enhancing epidural tumor extending from C-1 to the C5–6 disc space with extension through the neural foramina along the C-2, C-3, C-4, and C-5 nerve roots on the left side (Fig. 1). There was severe cord compression at the C-3 level.

Operations. The patient underwent a posterior midline approach for a C2–6 laminoplasty. On elevation of the laminae, a large, firm, dark reddish purple, relatively avascular epidural tumor was found. Intraoperative analysis of a frozen section sample showed a small, round, blue-cell tumor with some elements of cartilage, most consistent with a sarcoma. As the tumor was resected, the C-4 root was found to be entering the tumor. Once it was judged that all of the intraspinal components had been removed, a partial resection of the tumor that was exiting the foramen was performed, but was stopped to prevent injury to the vertebral artery. Postoperatively, the patient had worsening of left arm monoparesis with flaccid tone. He was discharged home on postoperative Day 4.

Delayed postoperative MR imaging revealed residual tumor ventrolateral to C-2 and C-3 (Fig. 2). After careful deliberation and in light of the pathological analysis (see below), the decision was made to reoperate. Two weeks after the initial operation, surgical exploration was performed with subtotal resection of the residual tumor, leaving some tumor along the nerve roots and ventral to the spinal cord. There was no change in the patient’s neurological status.
Pathological Evaluation. The tumor sample consisted of a poorly differentiated malignant spindle-cell component interspersed between numerous lobules of atypical-appearing cartilage. Within the spindle-cell component were clusters of mature ganglion cells and nerve twigs. Mitoses in the spindle-cell component were 6 per 10 hpf, and they stained positive for Ki 67 and S100 protein, but negative for synaptophysin and GFAP. The tumor was thought to most closely resemble an MPNST.

Postoperative Course. The patient received an individualized chemotherapy protocol consisting of 5 cycles of ifosfamide for 5 days followed by doxorubicin with dexrazoxane for 2 days. At his last follow-up 46 months after the completion of therapy, he was doing well, with stable residual disease in the spinal canal and stable non-specific soft-tissue enhancement along the C4–5 nerve roots. On neurological examination, he had mild weakness involving the left arm and no other deficits.

Case 2

History and Presentation. This previously healthy 17-year-old boy presented with low back pain after a wrestling match that had gradually worsened over several weeks and was accompanied by the development of pain in his left leg and buttock. The patient denied numbness, weakness, or urinary or bladder disturbances. His pain markedly worsened if he was supine such that he had to sleep sitting up. On examination the patient had limited trunk flexion and lateral bending because of pain, and positive ipsilateral and crossed straight-leg raise tests at 10°. The rest of his neurological examination was normal. A large, heterogeneously enhancing, cystic intradural tumor almost completely filling the spinal canal below the level of the medullary conus (L2–5) was observed on MR imaging.

Operation. The patient underwent an L2–S1 laminectomy. A well-encapsulated, firm tumor was identified after the dura mater was opened. It had displaced the nerves of the cauda equina ventrally and dorsally. These were easily dissected off the tumor. The filum terminale was identified and appeared to enter the tumor. The tumor was removed en bloc, but after this was performed, 3 separate satellite deposits were located inferiorly, including an en plaque lesion adherent to the ventral dura and surrounding nerve roots. A subtotal resection of these secondary sites was then performed, and the wound was subsequently closed. Intraoperative analysis of a frozen specimen was consistent with myxopapillary ependymoma. The patient recovered well postoperatively and was discharged on postoperative Day 7.

Pathological Evaluation. The tumor had areas of high cellularity admixed with areas of myxoid degeneration. The cellular regions were spindly and focally epithelioid, with necrosis and a high mitotic index (average 16/10 hpf, range 7–41/hpf). The tumor appeared to surround tiny peripheral nerve twigs as well as individual myelinated axons. There was focal immunopositivity for GFAP and cytokeratin, and rare positivity for S100 and EMA. The tumor was determined to be an MPNST.

Postoperative Course. The patient’s back and left leg pain resolved. Metastatic workup was negative. The patient was placed on 3 cycles of ifosfamide, doxorubicin, and Mesna. Repeated MR imaging after chemotherapy showed a focal area of enhancement at L-2, and the patient underwent involved field radiotherapy to a total dose of 5800 cGy. Unfortunately, 8 months after surgery and 3 months after the conclusion of radiation, he presented with new-onset lower-extremity weakness and urinary retention. Magnetic resonance images revealed widely disseminated disease intracranially, as well as along the spinal cord, with a 3.5-cm ventral mass at T5–6 causing spinal cord compression (Fig. 3). The patient was started on palliative spinal radiation therapy, dexamethasone, and oral etoposide. He retained full strength in his extremities without any sensory abnormalities. He continued to decline neurologically, with documented growth of the lesions on subsequent MR images, and soon died.

Case 3

History and Presentation. This 10-year-old, previously healthy boy presented with right leg pain that had
lasted for several months in an L-4 distribution. His neurological examination was normal except for severe pain and paresthesias in his right leg. Magnetic resonance imaging revealed a dumbbell-type lesion that was homogeneously enhancing with a large intraspinal component at L-4, and extension out the right L4–5 foramen along the L-4 nerve root (Fig. 4). There was no evidence of dissemination.

Operation. The patient underwent an L-4 laminectomy and partial laminectomies of L-3 and L-5. After the dura mater was opened, a well-encapsulated, vascular, pinkish tumor was found displacing the nerve roots of the cauda equina ventrally and dorsally. Internal debulking of the tumor was performed, followed by resection of the capsule. The motor and sensory components of the L-4 nerve root proximally were identified and found to be entering the tumor that was exiting the foramen; the motor component was spared. A second dural incision was made along the exiting L-4 nerve root. The tumor was found to be filling the nerve root sheath, still sparing the motor component. The tumor in the nerve root sheath was resected incompletely because it was more fibrous and adherent to the surrounding structures, and we feared that further resection or complete resection of the pars interarticularis to gain the necessary exposure would render the patient’s spine unstable. He recovered well from his surgery.

Pathological Evaluation. The tumor was consistent with an Ewing sarcoma, with abundant small, blue cells, immunoreactivity for membranous CD99, and focal synaptophysin positivity. The lesion was nonreactive to S100 and CAM 5.2.

Postoperative Course. After recovering from surgery, the patient was started on cycles of vincristine, Adriamycin (doxorubicin), and cyclophosphamide alternating with VP-16 and ifosfamide. Because of concern for residual disease along the L-4 nerve root, he also received local radiation therapy to L3–5 to a total dose of 5040 cGy, and proceeded to further chemotherapy for a total of 14 cycles. At the time of his last evaluation, 12 months after completion of therapy, there was no evidence of disease on MR images and he was neurologically intact.

Discussion

The 3 cases we have discussed in the present study have several unique features. Primary intraspinal sarcomas are a rare entity in general, but are exceedingly rare in children. There has been only 1 other report of a child with an intradural Ewing sarcoma associated with a spinal nerve root. With respect to the 2 children with MPNSTs, 1 patient fortunately remains alive almost 4 years after the diagnosis, and neither child had neurofibromatosis. There are only 2 other reports of children with spinal MPNSTs without NF1.

Management of these tumors can be challenging because of their aggressive nature. Therapy for both types of sarcomas is multimodal, with MPNSTs having a worse prognosis in general than EFSTs. At our institution, and consistent with the currently available body of evidence, we recommend resection followed by chemotherapy, with adjuvant radiation therapy when appropriate to the patient’s clinical trajectory and age. Because oncological resection is often not possible because of the proximity of the lesion to critical neural structures, follow-up chemotherapy and targeted radiation therapy are key complements to the surgical approach. As observed in Case 2, surgical control of intraspinal lesions can often be hampered by their tendency to metastasize throughout the neuraxis. In our 3 cases, resection was augmented with chemotherapy. We used radiation therapy in 2 cases, forgoing it in Case 1 because of the patient’s age. Nevertheless, this patient continues to do well 46 months after treatment.

A review of the literature on MPNSTs and Ewing sarcoma involving the spine is presented below, focusing on treatment and prognosis.

Malignant Peripheral Nerve Sheath Tumors

Malignant peripheral nerve sheath tumors are usually described as arising from peripheral nerves, plexuses, or rarely from spinal roots. Although large MPNSTs found in the thoracic or abdominal cavities have been reported occasionally to encroach on the spine, primary intraspinal MPNSTs as seen in Cases 1 and 2 are very rare. The majority of cases that have been described have occurred within the cauda equina and were predominantly in adults (Table 1). Isolated cases of primary intradural MPNST with NF1, intradural MPNST without NF1, and extradural intraspinal MPNST with NF1 have been reported. Only 2 cases of pediatric patients with primary intraspinal MPNSTs without NF1 have been reported in addition to the patients presented here.

![Fig. 4. Case 3. Axial (A) and sagittal (B) T1-weighted contrast-enhanced images and T2-weighted sagittal (C) and coronal (D) images showing a large intradural tumor that extends along the exiting right L-4 nerve root through the L4–5 neural foramen. Note that the tumor has greatly expanded the dorsal root ganglion, compared with the normal left-sided ganglion.](image-url)
TABLE 1: Treatment and outcome in patients in the literature with primary intraspinal MPNSTs

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>Patient Age (yrs), Sex</th>
<th>Neurofibromatosis Status</th>
<th>Lesion Location</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albayrak et al., 2006</td>
<td>25, M</td>
<td>NF1 present</td>
<td>T1–2, intradural</td>
<td>yes, complete</td>
<td>recurrence at 7 wks requiring reop w/ GTR</td>
</tr>
<tr>
<td>Acharya et al., 2001</td>
<td>32, M</td>
<td>absent</td>
<td>L2–4, intradural</td>
<td>yes, partial</td>
<td>unknown</td>
</tr>
<tr>
<td>Yone et al., 2004</td>
<td>4, M</td>
<td>absent</td>
<td>L3–5, intradural</td>
<td>yes: complete after 1st op; partial at recurrence</td>
<td>local recurrence at 4 mos requiring reop; distant metastasis at 6 mos, &amp; death at 21 mos</td>
</tr>
<tr>
<td>Valdueza et al., 1991</td>
<td>3F &amp; 2M patients, ages 18–70 yrs</td>
<td>NF1 present in 1</td>
<td>cervical (in 3), thoracic (in 2), intradural (in 4), &amp; extradural (in 1)</td>
<td>yes: complete in 3, partial in 2</td>
<td>local recurrence in 3; 1 patient died at 18 mos postop</td>
</tr>
<tr>
<td>Seppala &amp; Halita, 1993</td>
<td>3F &amp; 3M patients, ages 13–45 yrs</td>
<td>NF1 in 2 &amp; NF2 in 1</td>
<td>cervical (in 1), thoracic (in 1), lumbar (in 3), sacral (in 1), intradural (in 2), extradural (in 1), &amp; combination (in 3)</td>
<td>yes: complete in 4, partial in 2</td>
<td>local recurrence in all; all died 2 mos to 6 yrs after diagnosis</td>
</tr>
<tr>
<td>Thomeer et al., 1981</td>
<td>42, M</td>
<td>absent</td>
<td>lumbar &amp; intradural</td>
<td>yes, complete</td>
<td>alive w/ disease at 3 yrs</td>
</tr>
</tbody>
</table>

* chemo = chemotherapy; GTR = gross-total resection.

Malignant peripheral nerve sheath tumors have a high propensity for local recurrence and distant metastases and thus have poor survival rates. Recurrence rates for all patients with MPNSTs range from 32 to 65% after intervals of 5–32 months, with 62% survival at 3 years, and 43.7% at 5 years; the median survival is 45 months. In a study of 24 children with MPNST of all locations (age range from 3 months to 18 years) by Raney et al., the proportion of tumor-free survivors at the end of 3 years was 37.5%. Baehring et al. found that tumor diameter < 5 cm, gross-total resection, and younger age were favorable prognostic variables.

Survival in patients with spinal MPNSTs may be worse than for those harboring extraspinal MPNSTs, especially intradural tumors, because aggressive resection is difficult while maintaining neurological integrity, and leptomeningeal spread may develop as in Case 2. Seppala and Halita reported on 6 patients with spinal MPNSTs. Even after apparent total removal followed by radiotherapy, local recurrence and metastases, most commonly to the lung and liver, were the rule, and the average survival was 4.4 months. White reported on 4 patients (3 with lumbar lesions and 1 with cervical) with an average age of 30 years. Local excision was performed in all patients, and 3 also underwent a cordotomy and radiation. All patients died within 7 months. The details of other reports are outlined in Table 1. In contrast to these cases, the patient described in Case 1 is a rare long-term survivor (almost 4 years so far).

Current treatment for spinal MPNST is multimodal. Maximal cytoreductive surgery is indicated in patients without widespread disease, but this is often limited to prevent iatrogenic neurological injury and because of the propensity of these tumors to track along perineural planes a distance from the primary lesion site and become intimately associated with critical structures. The difficulties in excising these tumors were exemplified in our cases. Because of these limitations to surgery, adjuvant therapies are considered key.

Data have shown that adjuvant radiation therapy (typically 5000–6000 cGy applied in 25 fractions spread over 5 weeks) is beneficial in terms of survival in patients with tumors of the trunk and extremities. It is presumed that a similar beneficial effect exists for spinal MPNSTs, although this is less clear from the available data. Furthermore, radiation doses for the spine should not exceed the limit of cord tolerance (4500 cGy) to avoid radiation-induced myelopathy. Valdueza et al. believed that surgery combined with 14 MV neutrons to 10–40 Gy postoperative radiation was the preferred treatment in patients in whom resection was not possible. One of our patients received radiation for residual disease, but the youngest patient did not because of his age (8 months).

Malignant peripheral nerve sheath tumors typically do not respond well to chemotherapy. Regimens have included Mesna, Adriamycin (doxorubicin), ifosfamide, and dacarbazine (MAID); a combination of etoposide, ifosfamide, and Mesna; or the use of methotrexate alone. Although chemotherapy has been used for intradural MPNSTs, its role in ultimate treatment outcome for these patients remains unclear. Both cases described above, the patients received a regimen con-
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containing ifosfamide and doxorubicin, with the addition of Mesna in Case 2; however, there was a stark difference in survival between the 2 patients.

Ewing Sarcoma Family of Tumors

The ESFTs encompass previously distinct lesions including Ewing sarcoma, EES, and primitive neuroectodermal tumor, all of which have been shown to be linked by morphological, immunohistochemical, and cytogenetic characteristics. The ESFTs are united by their common gene translocation (11;22)(q24;q12), which results in a chimeric transcript from the fusion of the EWS gene and the transcription factor FLI1. In addition to histological similarity and the EWS-FLI1 fusion product, these tumors share immunoreactivity for CD99, an antigen determined by the MIC2 gene. The CD99 molecule is expressed in almost all cases of ESFT, but is negative in other small-cell tumors.

The tumor in our patient (Case 3) was best classified within the ESFT spectrum as an EES. In a large, multicenter and multinational study of 1505 patients with lesions classified into the ESFT, EES lesions represented only 8% of the cases, with 87% of these patients ultimately diagnosed with Ewing sarcoma. Extraskelatal Ewing sarcomas of the nonsacral spine are even less common, representing ~ 0.9% of cases. The reported 5-year survival in patients with EESs and osseous Ewing sarcomas are similar, with rates of 61 and 50.6%, respectively.

Age younger than 16 years and aggressive resection were found to be important prognostic variables for EES. Patients with spinal EES typically present with back pain and symptoms of myelopathy with weakness, decreased sensation, and autonomic dysfunction. Spinal EES usually arise from the epidural space or paravertebral soft tissue with secondary spinal involvement.

Several cases of intradural sarcomas associated with spinal nerve roots, including synovial sarcoma and clear cell sarcoma, have been reported. Primitive neuroectodermal tumors, which are part of the ESFTs, have also been described arising from a spinal nerve root. The imaging features in the case reported by Isefuku et al. are nearly identical to those we observed in our patient. Our case and that of a 14-year-old boy with a cauda equina tumor reported by Hisaoka and colleagues represent the only pediatric examples of intradural EES.

Surgical intervention is mandatory for spinal decompression and histopathological identification of the tumor, but adjuvant therapy is always required. Radiotherapy and chemotherapy can further slow the spread of the disease, although local recurrence and distant metastasis are still common. Currently, these regimens include vincristine, cyclophosphamide, and doxorubicin, with the addition of ifosfamide and etoposide when the patient has certain risk factors such as increased tumor volume or metastasis. Tumors unresponsive to this therapy can subsequently be challenged with the addition of busulfan. We elected to use cycles of vincristine, cyclophosphamide, and doxorubicin, alternating with ifosfamide and etoposide. Radiation therapy has been shown to provide good local control in nonmetastatic disease, including in spinal ESFTs, at doses of 30–60 Gy with hyperfractionation showing some benefit.

Conclusions

We presented 3 unique spinal sarcomas: 2 primary MPNSTs in patients without neurofibromatosis, and a case of primary extraosseous Ewing sarcoma arising from the sensory component of a lumbar spinal nerve. Notable for all of these lesions are their primary intraspinal origin (1 extradural and 2 intradural), extremely rare occurrence in the pediatric population, and, with respect to the MPNSTs, lack of association with NF1 and long-term survival in 1 of our patients.

Despite the limitations caused by their proximity to critical neural structures and the propensity of these tumors to metastasize in the neuroaxis, aggressive surgical management with care to preserve neurological function in conjunction with adjuvant treatment provides the current best known outcomes for these rare but important intraspinal sarcomas of childhood.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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