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ORIGINAL ARTICLE

Malignant peripheral nerve sheath tumors presenting as spinal dumbbell tumors: clinical outcomes and characteristic imaging features

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Abstract
Purpose To investigate the clinical outcomes and imaging features of malignant peripheral nerve sheath tumors (MPNSTs) presenting as spinal dumbbell tumors.
Methods We retrospectively reviewed the clinical outcomes and imaging features of consecutive cases of spinal dumbbell MPNSTs ($n = 8$) and schwannomas ($n = 15$).
Results A maximal diameter >5 cm was more frequently seen in MPNSTs (88 %) than in schwannomas (14 %). Irregularly lobulated margins occurred frequently in MPNSTs (75 %), but not in schwannomas (21 %). Indistinguishable boundaries were observed in 63 % of MPNSTs, but only 7 % of schwannomas. Osteolytic bone destruction was found exclusively in MPNSTs (50 % of MPNSTs vs. 0 % of schwannomas).
Conclusions There is little clinical information relating to spinal dumbbell MPNSTs. We propose that the following imaging features are suggestive of spinal dumbbell MPNSTs: maximal diameter >5 cm, irregularly lobulated shape, boundary indistinguishable from surrounding tissues, and osteolytic bone destruction.

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Keywords Malignant peripheral nerve sheath tumor (MPNST) · Spinal tumor · Dumbbell tumor · Imaging characteristics

Introduction

Malignant peripheral nerve sheath tumors (MPNSTs) account for 3–10 % of all soft tissue sarcomas [1]. The most common locations for MPNSTs are the trunk, limbs, head, and neck [2]. However, spinal MPNSTs have rarely been reported [3]. MPNSTs have high metastatic potential and surgical resection is the curative treatment of choice for resectable MPNSTs, whereas no effective systemic therapy is currently available [4]. Thus, prognosis of unresectable or metastatic MPNSTs is extremely poor, particularly in the spinal region where the associated mortality rates are as high as 80 % [5].

Spinal MPNSTs can arise from dumbbell tumors, which were first defined by Heuer [6]. Because of their unique location, dumbbell tumors differ from common intradural-extramedullary tumors in terms of their clinical features and treatment strategies. In one study, dumbbell tumors comprised 18 % of 674 spinal cord tumors [7]; schwannomas were most common (69 %) and only one case of spinal dumbbell MPNST was found [7]. It remains unclear what imaging findings best distinguish between spinal dumbbell MPNSTs and schwannomas.

In the present report, we retrospectively reviewed the clinical outcomes of eight patients with spinal dumbbell MPNSTs. We also compared the characteristic imaging features of a spinal dumbbell MPNST and a conventional benign dumbbell Schwannoma on magnetic resonance imaging (MRI) and computed tomography (CT), with the aim of improving the accuracy of discriminating these tumors preoperatively.

Materials and methods

Clinical data

Our institutional review board approved this retrospective study. We retrospectively reviewed the clinical data and surgical records for consecutive cases of spinal dumbbell MPNSTs ($n = 8$) and schwannomas ($n = 15$). The following details were obtained from each patient's medical records: demographic details, disease history, imaging findings, tumor pathology, surgical details, and postoperative tumor recurrence and survival. Specimens were obtained for evaluation from all patients, and the histopathological analysis was used to establish the final diagnosis. Pathological grading of MPNSTs was performed by independent and experienced pathologists in accordance with the criteria described by Ducatman et al. [2]. Tumors were classified as high grade or low grade. High-grade tumors are characterized by fasciculated cells with hyperchromatic nuclei and frequent mitotic figures. Low-grade tumors are characterized by decreased cellularity and fewer hyperchromatic cells, mitotic figures and tumor necrosis compared with high-grade tumors.

Review of radiographical images

MRI and CT were performed on all patients. Two spinal surgeons with more than 5 years of experience in spinal tumor imaging diagnosis independently reviewed all MRI and CT images and recorded the tumor characteristics. The following imaging features were recorded: tumor size, tumor location, tumor shape, tumor boundary, tumor density/intensity, tumor intensity, enlargement of neural foramina and bone destruction. We compared the prevalence of characteristic features in spinal dumbbell MPNSTs and schwannomas. Correlation between the presence of imaging features indicative of spinal dumbbell MPNSTs was evaluated by calculating sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for each feature.

Statistical analysis

Survival estimates were determined by Kaplan–Meier analysis. To determine which imaging features were associated with spinal dumbbell MPNSTs, statistical analysis was performed using Fisher's exact test, and differences with $p < 0.05$ were considered to be statistically significant. All statistical analyses were performed with the JMP software program (version 9.0.1, SAS Institute).

Results

Clinical features and outcomes of MPNSTs arising from dumbbell tumors

We examined eight cases of primary spinal MPNSTs arising from dumbbell tumors (5 males and 3 females). Patient ages at symptom onset ranged from 2 to 71 years; the mean age was 43.3 ± 25.4 years (mean ± standard deviation). Tumor locations included the cervical vertebra ($n = 2$), thoracic vertebra ($n = 2$), lumbar vertebra ($n = 3$), and sacral vertebra ($n = 1$). According to Eden's classification, five patients were classified as type III, two as type IV, and one as type II. Based on the McCormick scale [8], three cases were grade I, two were grade II and three were grade III. All cases were primary lesions and four patients had associated neurofibromatosis type I.

Six out of the eight cases were managed with surgery (75 %). En bloc resection with a wide margin was carried out in only one patient (16.7 %), while in one case (16.7 %) a marginal margin was achieved. Four cases underwent intralesional resection (66 %). Histological findings confirmed the diagnosis of MPNST in all patients. In HE specimens, tumor cells were symmetrically tapered spindle cells with irregular buckled nuclei, marked nuclear atypia, increased cellularity with nuclear enlargement, and hyperchromasia. Malignancy was graded as low in two cases (25 %) and high in six cases (75 %). According to the Enneking surgical staging [9], two patients were classified as type IB and six as type IIB. Chemotherapy consisting of adriamycin and ifosfamide was given to two patients with no obvious response. Four patients received radiotherapy, three received postoperative and/or palliative conventional radiotherapy and one received carbon ion curative radiotherapy. Four patients with high-grade tumors experienced tumor recurrence, while the two patients with low-grade malignancies had no tumor recurrence at final follow-up. Distant metastasis was observed in four cases, two of these occurred in the lung and two were intraspinal or intracranial. Finally, five out of the eight patients died of disease at the final follow-up. The duration of survival ranged from 5 to 120 months, and the median survival time was 13 months. The 5-year survival rate was 50 % (Fig. 1). Clinical features and outcomes are summarized in Table 1.

Imaging features of spinal dumbbell MPNSTs

The prevalences of various imaging features of MPNSTs arising from dumbbell tumors are shown in Table 2. Maximal lesion diameters ranged from 2 to 11 cm; the mean maximal diameter was 6.9 ± 2.7 cm (Table 1). The

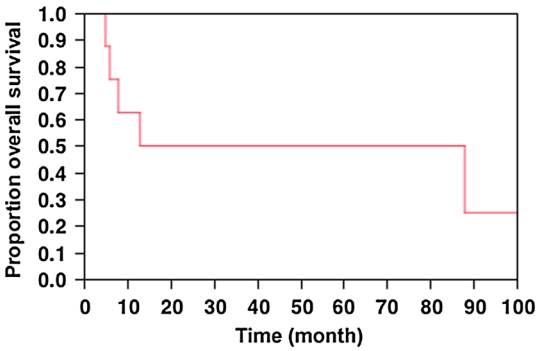

Fig. 1 Kaplan–Meier survival curve for eight cases with spinal dumbbell MPNSTs, showing a median survival duration of 13 months

maximal diameters of seven cases were greater than 5 cm (Table 2). In terms of tumor shape, six cases were irregularly lobulated and two cases were circular. The tumor border was well defined in three cases and poorly defined and indistinguishable from surrounding tissues in five cases. Osteolytic bone destruction due to tumor invasion occurred in four cases with no concomitant irregular bone formation. Enlarged neural foramina were observed in six cases (Table 2). Assessment of tumor intensity on MRI was also investigated. On T2WI, a mixed signal pattern with dominant hyperintensity was observed in eight cases. Meanwhile, on T1WI, the mass was isointense in two cases and demonstrated mixed signal characteristics in the remaining six cases. All tumors showed heterogeneous enhancement. On CT, the tumor presented with hypodensity in three cases, isodensity in three cases, and mixed density in two cases.

Differences in imaging characteristics between spinal dumbbell MPNSTs and schwannomas

To discriminate between dumbbell MPNSTs and schwannomas, characteristic imaging features of the two tumor types were compared (Table 3). A maximum diameter greater than 5 cm was seen significantly more frequently in MPNSTs (87.5 %) than in schwannomas (13.3 %), resulting in high diagnostic accuracy for identifying MPNSTs (sensitivity 87.5 %, specificity 86.7 %, PPV 77.8 %, NPV 92.3 %, $p = 0.001$). Regarding tumor shape, irregularly lobulated tumors were seen more frequently in MPNSTs than in schwannomas (sensitivity 75 %, specificity 80 %, PPV 66.7 %, NPV 85.7 %, $p = 0.023$). In addition, a boundary that was indistinguishable from surrounding tissues was observed in 62.5 % of MPNSTs but only 6.7 % of schwannomas (sensitivity 62.5 %, specificity 93.3 %, PPV 83.3 %, NPV 82.4 %, $p = 0.009$). Osteolytic bone destruction was seen exclusively in MPNSTs (50 % of MPNSTs vs. 0 % of schwannomas; sensitivity 50 %, specificity 100 %, PPV 100 %, NPV 78.9 %, $p = 0.079$). Remarkably, enlargement of neural foramina was not helpful in differentiating MPNSTs from schwannomas (Table 3). Regarding density on CT and tumor intensity and contrast enhancement on MRI, no specific findings distinguished MPNSTs from schwannomas. Taken together, the imaging features suggestive of MPNSTs were as follows: maximum diameter greater than 5 cm, irregularly lobulated shape, indistinguishable boundary from surrounding tissues, and osteolytic bone destruction.

Case presentation

Case 8

A spinal dumbbell MPNST in the lumbar spine (Eden's type IV) was diagnosed pathologically in a 35-year-old man. His chief complaint was a painful mass in the left lower back. Examination showed no neurologic deficits. The mass was 9.2 cm in size, and the lesion was isodense on CT with osteolytic bone destruction in the left

Table 1 Clinical and pathological features of eight patients with MPNSTs presenting as spinal dumbbell tumors

Case	Age/sex	Location	Eden's classification	McCormick scale	Size (cm)	NF	Histological grade	Enneking	Treatment	Follow-up (mos)	Outcome
1	42/M	Cervical	II	II	6.3	No	High	IIB	Op, Rtx	10	DOD
2	71/F	Lumbar	IV	III	6.2	No	High	IIB	Rtx	22	AWD
3	21/M	Lumbar	III	I	8.1	NF1	Low	IB	Op	120	CDF
4	70/M	Thoracic	III	III	5.5	NF1	High	IIB	Op	5	DOD
5	2/F	Thoracic	III	III	7	No	High	IIB	Op	88	DOD
6	37/M	Sacrum	III	I	11	NF1	High	IIB	Ctx, Rtx	8	DOD
7	69/F	Cervical	III	II	2	No	Low	IB	Op	84	CDF
8	35/M	Lumbar	IV	I	9.2	NF1	High	IIB	Op, Ctx, Rtx	13	DOD

NF neurofibromatosis, *Enneking* Enneking surgical staging, *Op* operation, *Rtx* radiotherapy, *Ctx* chemotherapy, *DOD* died of disease, *AWD* arrived with disease, *CDF* continuous disease free

Table 2 Radiological features of eight patients with MPNSTs presenting as spinal dumbbell tumors

Feature	No. of cases
Size	
<5 cm	7
>5 cm	1
Shape	
Circular	2
Irregularly lobulated	6
Boundary	
Distinguishable	3
Indistinguishable	5
Osteolytic bone destruction	4
Enlargement of neural foramen	6
Intensity on MRI	
T2WI-mixed	8
T1WI-iso	2
T1W1-mixed	6
Density on CT	
Hypo	3
Iso	3
Mixed	2

transverse process of L3 (Fig. 2a, arrows). Axial T2-weighted MRI showed a mass of mixed signal intensity with unclear boundaries (Fig. 2b, arrowheads) and irregular lobulation (Fig. 2b, arrows). Coronal contrast-enhanced T1-weighted MRI revealed a non-homogeneously enhanced mass encompassing a visible non-enhanced lesion (Fig. 2c, asterisk). The surrounding soft tissue was also non-homogeneously enhanced (Fig. 2c, arrows). Local osteolytic destruction of the left pedicles of L2 and L3 was also seen (Fig. 2c, arrow heads). A combined posterior and lateral approach was used to remove the tumor, and the surgical margin was negative. Postoperative pathology showed the proliferation of spindle cells arranged in a fascicular pattern with nuclear atypia, confirming the diagnosis of MPNST (Fig. 2d). 3 months after surgery, local recurrence of the tumor was observed with distant lung metastasis. There was no response to chemotherapy or radiotherapy. The patient died 13 months after surgery.

Discussion

Spinal tumors are commonly divided into four categories based on location: intramedullary, intradural extramedullary, epidural, and dumbbell [10]. Because of their diverse locations, dumbbell tumors have specific features, clinical symptoms, and pathological characteristics that differ from other spinal tumors. Eden [11] reported that dumbbell tumors comprise 13.7 % of spinal tumors. In addition, Ozawa et al. [7] reported that of 118 dumbbell tumors, 81 (69 %) were schwannomas and 10 (8.5 %) were malignant, but their cohort contained only one case of spinal dumbbell MPNSTs. MPNSTs rarely cause spinal lesions, and the clinical knowledge about them remains poor [12].

Surgical resection is the treatment of choice for MPNSTs [5]. Tumor resectability depends largely on tumor location, and was found to range from 83 % in 128 patients with non-spinal MPNSTs to 20 % in spinal MPNSTs [13, 14]. Indeed, en bloc resection of spinal lesions is often very difficult or impractical because of the complexity of the vertebrae and surrounding tissues, including the spinal cord and large blood vessels. In addition, preoperative histological confirmation of the presumed diagnosis is mandatory for curative surgery of malignant bone and soft tissue tumors. However, biopsy of tumors located in the spine in a non-contaminating fashion is difficult. Thus, we believe that making an accurate preoperative diagnosis based on imaging findings would be helpful for treating spinal malignant tumors such as MPNSTs.

Imaging studies, including MRI, have been thought to have limited value in terms of distinguishing MPNSTs from benign and conventional schwannomas [15]. Several recent studies suggested that a diagnosis of MPNST should be considered in spinal tumors with the following

Table 3 Imaging features predictive of MPNSTs presenting as spinal dumbbell tumors

Feature	Group						
	MPNST	Schwannoma	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	*p* value
Size >5 cm	7/8	2/15	87.5	86.7	77.8	92.3	0.001
Shape: irregularly lobulated	6/8	3/15	75	80	66.7	85.7	0.023
Boundary: indistinguishable	5/8	1/15	62.5	93.3	83.3	82.4	0.009
Bone destruction	4/8	0/15	50	100	100	78.9	0.079
Enlargement of neural foramen	6/8	13/15	75	13.3	31.6	50	0.589

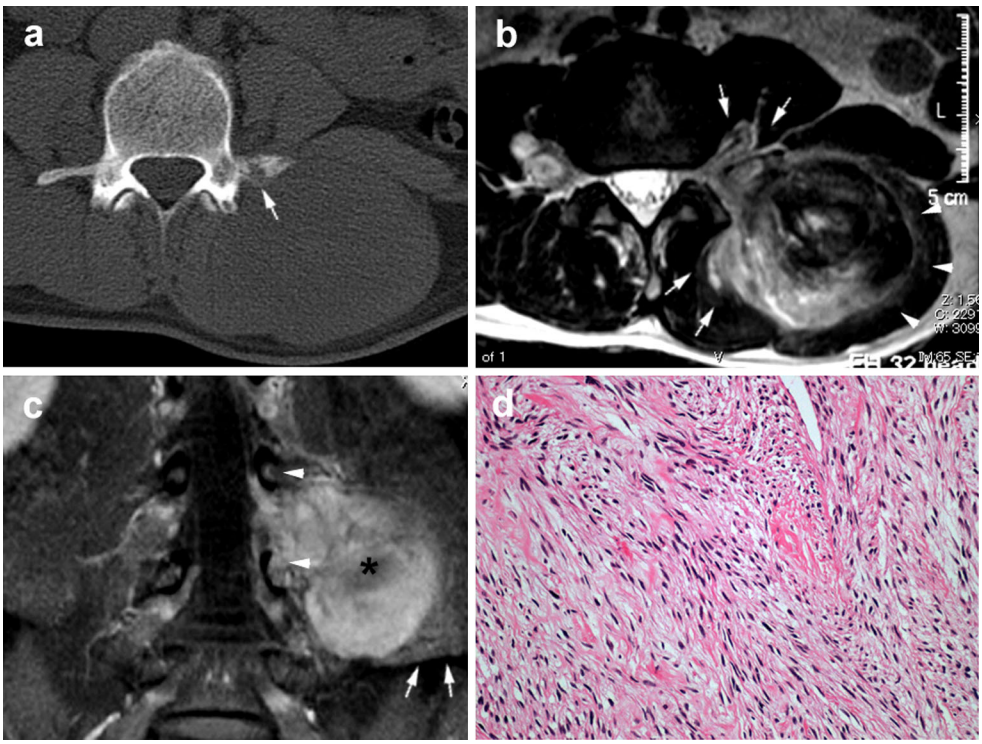

Fig. 2 Case 8. A spinal dumbbell MPNST in a 35-year-old man. **a** Bone window of axial CT revealed an isodense mass with a 9.2-cm diameter. Osteolytic bone destruction in the left transverse process of L3 was observed (*arrows*). **b** Axial T2-weighted MRI showed a mixed intensity signal mass with unclear boundary (*arrow heads*) and irregular lobulation (*arrows*). **c** Coronal contrast-enhanced T1-weighted MRI showed a non-homogeneously enhanced mass encompassing a non-enhanced lesion (*asterisk*). The surrounding soft tissue was also non-homogeneously enhanced (*arrows*). Osteolytic destruction of left pedicles of L2 and L3 was clearly visible (*arrow heads*). **d** Postoperative pathology confirmed the diagnosis of MPNST. H&E, original magnification ×200

characteristics: (1) large size (>5 cm) and an increase in size of previously stable neurofibromas; (2) inhomogeneous intensity, ill-defined tumor boundary, and perilesional edema on MRI [5]; and (3) extensive and obvious destruction of adjacent bones [16]. In this study, we systematically reviewed the imaging features of spinal dumbbell MPNSTs and schwannomas, confirming that most of the previously reported features were more frequently observed in MPNSTs. Furthermore, irregularly lobulated tumors were more likely to be spinal dumbbell MPNSTs. In contrast, foraminal enlargement with sclerotic margins and specific patterns of intensity (MRI) or density (CT) were not useful for determining features of tumor malignancy. Although spinal dumbbell MPNSTs lack a single specific radiological manifestation, we propose that the combination of the above-mentioned imaging features may facilitate the correct preoperative diagnosis of a spinal dumbbell MPNST.

Staging has an important role in determining the effective treatment for bone and soft tissue sarcoma. There are currently two established staging systems used to classify bone and soft tissue sarcoma and to make better treatment planning. The American Joint Committee on Cancer (AJCC) has designated staging by the four criteria of tumor size, lymphonodal status, metastasis, and histological grade. In particular, the size of the tumor has been implicated as an important prognostic factor for soft tissue sarcomas. Larger lesions may be more likely to relate with high malignancy, corresponding with this study. However, at this time, AJCC does not have a staging system for spinal cord tumors including spinal dumbbell tumor. Meanwhile, Enneking first introduced a classification system for primary long-bone tumors [9]. In the Enneking classification, the tumor is staged by its pathology, anatomic extent and presence of metastasis. Although the system has been adapted for spinal tumors, it might not be the suitable classification system for such tumors, since it lacks consideration for the extradural spinal involvement and possible cord compression, and may not relate to prognosis. In this study, two cases out of eight cases were assigned as Enneking stage IB and both of the cases showed better prognosis. Therefore, we consider that the Enneking classification would be useful for spinal dumbbell tumors.

In some cases, it would be difficult to distinguish a spinal dumbbell MPNST from other benign tumors within

the spinal canal such as giant invasive spinal schwannomas (GISS), intraosseous schwannoma, and ganglioneuroma. GISS are defined as tumors that extend over more than two vertebral levels, with vertebral body erosion and posterior and lateral extension into the myofascial planes, based on imaging findings [17]. GISS have often attained an enormous size by the time they are discovered and are often accompanied by moderate to massive bone scalloping and the presence of neural foramen widening. Intraosseous schwannomas are rare benign neoplasms that account for less than 0.2 % of primary bone tumors [18]. The radiological characteristics of an intraosseous Schwannoma is a lytic defect with cortical erosion and no periosteal new bone formation, and central calcification within the tumor [19]. Although an intraosseous Schwannoma is clearly encapsulized, as the tumor grows it can breach the cortex, possibly through a natural orifice such as a nutrient foramen [20], resulting in an expansile osteolytic lesion compatible with a spinal dumbbell MPNST.

Ganglioneuromas are benign, well-differentiated tumors arising from the neural crest cells of the embryo. These cells are migratory and give rise to various parts of the sympathetic and parasympathetic nervous systems, therefore ganglioneuromas can arise around paraspinal lesions [21]. As a result, ganglioneuromas should be included in the differential diagnosis of an enlarging dumbbell-shaped mass in the spinal canal extending through a neural foramen. On CT, ganglioneuromas characteristically appear as oval or lobulated well-defined masses with discrete punctuate calcification [22, 23]. In the case of ganglioneuromas in the pre-sacral region, extensive osteolytic bone destruction of the sacrum may be seen [21]. MRI characteristically shows low signal intensity on T1-weighted images and heterogeneous high signal intensity on T2-weighted images [22]. Since GISS, intraosseous schwannomas, and ganglioneuromas share several imaging characteristic features with spinal dumbbell MPNST, histopathologic examination of biopsy specimens is often required for preoperative diagnosis.

Radiotherapy has been used as either definitive or adjuvant therapy for patients with spinal sarcomas who are unsuitable candidates for curative surgical resection. In the case of photon beam therapy (PBT), the irradiation doses are limited to those tolerated by the spinal cord, that is, approximately 50 Gy using standard fractionation [24]. In contrast, Wong et al. [13] suggested that radiotherapy with doses higher than 60 Gy is effective for local control of MPNST, and that this local, high-dose radiation may induce radiation myelopathy in patients with spinal MPNSTs. Carbon ion radiotherapy (CIRT) is an attractive alternative to PBT with a report of superior treatment outcomes and dose distribution compared with PBT [25]. Matsumoto et al. reports that the 5-year local control, overall survival, and progression-free rates of CIRT for primary spinal sarcomas were 79, 52, and 48 %, respectively, and only one patient experienced a grade three late spinal cord reaction. Indeed, in this study, one patient with a spinal dumbbell MPNST who received CIRT was alive with no evidence of disease after 22 months of follow-up. Thus, CIRT appears to be both effective and safe for the treatment of patients with unresectable spinal sarcoma, including MPNST.

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