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CLINICAL STUDY

Treatment and outcome of malignant giant cell tumor in the spine

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Abstract Malignant giant cell tumor (MGCT) in the spine is extremely rare and there is little published information regarding this subject in the literature. We attempted to correlate different treatment options and outcomes over time. A retrospective study of patients with spinal MGCT who were surgically treated in our center between 2006 and 2012 was performed. Overall, three surgical management strategies, including subtotal resection, piecemeal total resection, and total *en bloc* spondylectomy were applied. Postoperative radiotherapy was carried out in 4 cases. Clinical data and efficacy of surgical treatment strategy were analyzed via chart review. A total of 14 patients with spinal MGCT were included in the study. Three cases were diagnosed as primary MGCT (PMGCT), while the other 11 patients were secondary MGCT (SMGCT). The mean follow-up period was 41 (range 3–75) months. Recurrence was found in 7 patients after surgery in our center, while distant metastasis and death occurred in 4 and 6 cases, respectively. MGCT of bone is always a high-grade sarcoma with a poor prognosis and complete excision, while also preserving neural function, is recommended. In our study, patients who underwent total *en bloc* spondylectomy had significantly lower local recurrence rate for MGCT in the spine.

Keywords Malignant giant cell tumor · Spine · Total *en bloc* spondylectomy · Retrospective study

Introduction

Giant cell tumor of bone (GCT) is an aggressive skeletal tumor that consists of three major cell types: osteoclast-like multinucleated giant cells, spindle-like stromal cells, and monocytic round cells [1, 2]. Although GCT is predominantly regarded as benign lesion, it has malignant potential and could completely transform into malignant one [11]. Only 1.4–9.4 % of GCTs appear in the spine and occur most commonly between the ages of 20–40 years, with a male-to-female ratio of 1:2.5 [1, 3–5].

Malignant giant cell tumor of bone (MGCT) accounts for 2–9 % of all GCT cases [6–8]. WHO used the term "malignancy in GCT" to describe MGCT and subdivided it into either primary or secondary [9]. Primary MGCT (PMGCT), which is often diagnosed at the time of first treatment, has a juxtaposition of conventional giant cell areas and pleomorphic spindle cell areas that are clearly malignant [10]. Secondary malignant giant cell tumor (SMGCT) is a high-grade sarcoma occurring as a recurrent

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lesion at the site of a benign GCT either after surgery, radiotherapy, or both [9, 11]. SMGCT is more common than PMGCT and mainly originates after irradiation treatment for the primary lesion [8, 12–16].

Due to the rarity of MGCT, there is only little published information in the literature, and there have been no reports of MGCT of the spine. The low incidence of spinal MGCT makes it difficult to define appropriate therapy and prognosis. There is no consensus regarding treatment recommendations of MGCT. Treatment protocols include surgery alone or surgery combined with chemotherapy or radiotherapy, but radical excision is considered to be associated with reduced recurrence rates of MGCT of bone [10]. However complete resection is difficult to achieve in the spine. In this series, a retrospective review of 14 cases with spinal MGCT that were treated with surgery at our center was performed, and to our best knowledge, represents the largest cohort reported to date.

Patients and methods

A total of 14 patients with spinal MGCT who were surgically treated and documented in our center were identified from April 2006 to December 2012. The diagnosis of MGCT was confirmed by an independent pathologist in all patients. The clinical and pathological data of all patients were retrieved from the previously maintained database of our center. This study was approved by Ethics Committee of our hospital and informed consent was obtained from the surviving patients or family members of those who had died.

Preoperative neurologic status was classified according to the Frankel score [17]. Tumor extension was described according to the Weinstein–Boriani–Biagini (WBB) system (except for one case with tumor in the sacrum evaluated by Enneking grading system) and Campanacci grading systems based on CT and MRI [18, 19]. All the patients accepted surgery in our center, and surgical strategy was decided for each patient according to WBB system and Enneking stage. A screw-rod system in combination with autologous or artificial bone grafts was used to reconstruct the stability of the spine for all the 14 cases, and an anterior titanium plate was also used for some patients with cervical lesion who were surgically treated in a combination of both posterior and anterior approach.

Postoperative radiotherapy (RT) which was used as adjuvant therapy was undertaken 4–6 weeks after surgery with the total dose ranging from 30 to 50 Gy [20, 21]. RT was forbidden for those with adequate radiation exposure before. Except one patient who was treated before 2007, 13 patients received one dose of intravenous bisphosphonate before surgery and one dose every month after surgery for 2 years [1].

All cases were advised to accept radiographic assessment by radiograph and CT/MR of the surgical segment as well as the adjacent vertebrae. Regular assessment were done at 0, 3, 6, and 12 months after surgery, every 6 months for the next 2 years, and then annually for life [22]. Follow-up data were obtained from office visits and telephone interviews. In the follow-up visit in 3 months after surgery, neural function was re-evaluated based on the Frankel score system. The follow-up period was defined as the interval from the date of surgery to death, or until June 2014 for patients alive.

Results

Patient features

The series was comprised of 4 men and 10 women, with a mean age of 35 (median 32, range 15–63) years old. Six cases (42.9 %) were between 20 and 40 years, while five patients (35.7 %) were more than 40 years. Three patients were admitted for PMGCT and the other 11 cases were SMGCT. Lesions were detected in the cervical spine (n = 4), thoracic spine (n = 8), lumbar spine (n = 1), and sacrum (n = 1) (Table 1).

Localized pain in the spine was the most consistent complaint. The duration of preoperative symptom was 1–25 months, with an average of about 8.2 months. Additional patient characteristics included 1 patients presented with a palpable mass, 2 patients had secondary aneurysmal bone cyst, 6 patients presented with radicular pain, and 8 cases had different degrees of cord compression at diagnosis (Supplementary Table 1). For the eight patients with spinal cord compression, three of them suffered incomplete paralysis and the other five patients presented with myelopathy.

Radiologic studies

The radiologic features of MGCT were similar to those of conventional GCT [11]. A radiographic appearance of osteolytic lesion by X-ray, Computed tomography (CT), and Magnetic resonance imaging (MRI) was found in the 14 cases. Cortical breakthrough and absence of well-circumscribed borders in CT images presented in all patients with MGCT. MRI revealed a common phenomena of soft tissue mass formation in the 14 patients, which was reflected by WBB system as extraosseous involvement (layer A) and epidural space involvement (layer D) (Fig. 1). A higher Campanacci stage was also found in

Table 1 Clinical data for a series of 14 MGCT cases in the spine

No	Age(y)/gender	Treatment history	DS (m)	LC	F-S pre	Staging*	Surgical approach	Resection mode	AT	Sarcoma type	FU (m)	LR (m)	DM (m)	Last status
1	29/F	OP	6	T11	C	1-12/A-D	P + A	Total	RT + BT	CHS	35	Yes (27)	Yes (31)	Dead (35)
2	34/M	OP + RT	24	T11	E	1-12/A-D	P	Subtotal	BT	OS	18	Yes (6)	Yes (12)	Dead (18)
3	54/F	OP + RT	24	S1-S2	D	G2T2M0	P	Subtotal	–	US	33	Yes (9)	No	Dead (33)
4	18/F	OP	2	T7	D	2-5/A-D	P	*En bloc*	BT	OS	75	No	No	NED
5	32/F	OP	1	C2	D	3-5/A-D	P + A	Total	BT	OS	64	Yes (3)	No	Dead (64)
6	15/F	OP	10	T10	C	2-4/A-D	P	*En bloc*	BT	OS	62	No	No	NED
7	56/F	–	1	C2	E	2-4/A-D	P	Total/p	RT + BT	US	56	No	No	NED
8[↑]	21/M	OP + RT	10	T5-7	D	1-12/A-D	P	Subtotal	BT	OS	59	Yes (34)	No	AWD
9[↑]	22/F	–	1	C6	D	11-2/A-D	P + A	Total	BT	US	39	No	No	NED
10	16/F	OP	25	T6	D	8-11/A-D	P	*En bloc*	BT	OS	43	No	No	NED
11	54/F	OP	6	C7	D	2-10/A-D	P + A	Total	RT + BT	MFH	35	Yes (18)	Yes (30)	Dead (35)
12	63/M	–	1	T8-9	D	2-5/A-D	P	Total	RT + BT	MFH	27	No	No	NED
13	32/M	RT	2	T3	C	4-7/A-D	P	*En bloc*	BT	US	24	No	No	NED
14	44/F	OP + RT	2	L5	D	1-12/A-D	P	Total	BT	US	3	Yes (3)	Yes (3)	Dead (3)
$\bar{x}$	35		8.2								41	14.3	19	31

MGCT malignant giant cell tumor, $\bar{x}$ mean, *y* year, *M* male, *F* female, *OP* operation, *RT* radiotherapy, *m* month, *DS* duration of preoperative symptom, *LC* location; *F-S* Frankel score, *pre* preoperation, *P* posterior, *A* anterior, *Subtotal* subtotal resection, *Total* piecemeal total resection, *En bloc* total *en bloc* spondylectomy, *AT* adjunctive therapy, *BT* bisphosphonate treatment, *CHS* chondrosarcoma, *OS* osteosarcoma, *US* undifferentiated sarcoma, *MFH* malignant fibrous histiotoma, *FU* follow-up, *LR* local recurrence, *DM* distant metastasis, *NED* no evidence of disease, *AWD* alive with disease

* Weinsteini–Boriani–Biagini staging was used in all cases, except Case 3 for which Enneking staging was used

[↑] Cases with secondary aneurysmal bone cyst

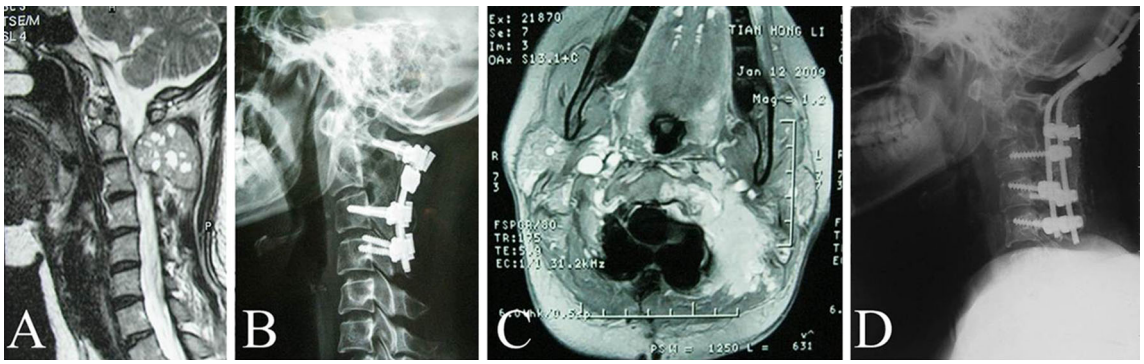

Fig. 1 Radiologic images of a patients with SMGCT (case, #5). **a** MRI image in June 2008 revealed a osteolytic lesion in vertebral body and the accessories of C2 (benign GCT). **b** Postoperative lateral radiograph in June 2008 showed the reconstruction performed from C1 to C4. **c** MRI performed in January 2009 exhibited soft tissue mass in C2 (malignant GCT). **d** Lateral radiograph after second surgery showed the reconstruction by occipitocervical fixation

MGCT in the spine: all the 14 patients were classified as Campanacci grade III [44].

Treatment history

Three patients, who did not receive surgical intervention and any other treatment before admission into our institution, were regarded as PMGCT. The other 11 patients had been diagnosed as benign GCT before and were admitted into our center for SMGCT in the spine: 6 of them received surgical resection; 1 patient (case. #13, Supplementary Table 2) was treated by radiotherapy (3 months before admission, total dose of 35 Gy in 15 fractions); 4 patients accepted both surgery and radiotherapy (case. #2, case. #3, case. #8, case. #14, Supplementary Table 2). Six patients with only surgical resection were regarded as postoperative SMGCT. The patient who was just treated by radiotherapy before admission was considered to be with radiation-associated SMGCT and radiotherapy was considered to be the main cause for the transition of benign GCT to MGCT. For the 4 patients with both surgical treatment and radiotherapy, the cause of the malignant transformation could not be easily confirmed (surgery, radiotherapy, or both) (Table 1).

Treatment and outcome

Needle biopsy was carried out on 3 cases with PMGCT, and intraoperative fast pathological examination was performed in all 14 cases. The results of intraoperative fast pathological examination were confirmed to be correct in 12 cases. However the result of needle biopsy consistent with the final pathological diagnosis was found in only one case (33 %, case, # 12), and the other two patients were misdiagnosed as benign GCT. Sampling error, small needle samples, or over-conservative judgment of pathologist might lead to the misdiagnosis.

Three different surgical strategies were pursued: subtotal resection, piecemeal total resection, and total *en bloc* spondylectomy. Subtotal resection was performed in 3 cases (case. #2, nearly 80 % resected; case. #3, approximately 90 % resected; case. #8, more than 95 % resected), piecemeal total resection was carried out in 7 cases, and total *en bloc* spondylectomy was undertaken in 4 cases (Table 1). Intraoperative blood loss ranged from 800 to 5000 (mean $\sim$2686) ml. Bisphosphonate treatment by either zoledronic acid or incadronate disodium which was used in our center since 2007 was applied in 13 patients. Postoperative RT was delivered with megavoltage beams, and the total dose ranged from 30 to 50 Gy, with the dose limits of 50 Gy for the spinal cord. It was performed in 4 cases (case. #1, case. #7, case. #11, case. #12, Supplementary Table 2).

For 8 patients diagnosed with spinal cord compression before surgery, their pain significantly alleviated or disappeared, and neurological status showed a decrease in Frankel scores of 1–2 grades by their 3-month follow-up visit. Local recurrence occurred in 7 patients, lung metastasis was found in 4 cases, and finally 6 patients died in the follow-up. Surprisingly, all those bad prognoses occurred in patients with SMGCT, and 3 cases with PMGCT were alive with no evidence of disease (NED). The treatment options and outcomes were listed in Table 2. Three patients with subtotal resection suffered progression of residual disease, and two of them died. Of the 7 patients with piecemeal total resection, 4 patients had local recurrence and finally died including 2 cases receiving postoperative RT. Howerver all the 4 patients who accepted total *en bloc* spondylectomy were alive with NED.

Table 2 Treatment protocols and outcome of MGCT in the spine

Treatment protocols	n	Local recurrence		Distant metastasis		Dead	
		n	%	n	%	n	%
Subtotal	3	3	100	1	33.3	2	66.7
Total							
Total	3	2	66.7	1	33.3	2	66.7
Total + RT	4	2	50	2	50	2	50
En bloc	4	0	0	0	0	0	0

MGCT malignant giant cell tumor, *subtotal* subtotal resection, *total* piecemeal total resection, *en bloc* total *en bloc* spondylectomy, *RT* radiotherapy

Pathology

Histologic diagnosis was obtained in all cases, and margins were submitted for pathological examination at the same time to decide further treatment. Reported sarcoma types in MGCT of bone include fibrosarcoma, osteosarcoma, malignant fibrous histiocytoma, undifferentiated high-grade pleomorphic sarcoma (UPS), and undifferentiated sarcoma [23–27]. In our series, chondrosarcoma was found in one case, malignant fibrous histiotoma was confirmed in 2 cases, osteosarcoma was found in 6 cases, and the rest 5 cases were considered to be with undifferentiated sarcoma (Fig. 2).

Discussion

Spinal MGCT is extremely rare with limited information in the literature. In this study, we analyzed the clinical and histological data of 14 cases with spinal MGCT, and reported our experience in the treatment of it. To our knowledge, this is the largest cohort about spinal MGCT by far.

Jaffe et al. firstly described malignant GCT (Jaffe Grade III), but the grading system is unable to predict the clinical behavior and prognosis of GCT [28]. Unni used the term "malignancy in giant cell tumor" to describe MGCT and subdivided it into primary or secondary, which was recorded as WHO recommendations [9, 15]. SMGCT can be further subdivided into two types: postsurgical and radiotherapy-associated, which are believed to have different etiologies but cannot be distinguished from each other on the basis of radiographic and histological presentation [7]. PMGCT is considered to be less common than SMGCT, and the similar finding (3 cases vs 11 cses) was achieved in our series. Further classification of SMGCT might be very difficult to be applied for patients previously treated with both surgery and radiotherapy.

Our cohort had a broad age demographic structure (range 15–63 years; mean 35 years). GCT in the spine occurs most commonly between the ages of 20–40 years, while patients with MGCT were thought to be older than patients with benign GCT [1, 15, 29]. The current study shows the same tendency with more than one third of patients more than 40 years old. Female gender predominance was also found in spinal MGCT in our series, which was similar with benign GCT in the spine.

Clinical and radiographic information are of limited value for the diagnosis of MGCT in the spine. The most frequent clinical feature of spinal MGCT was localized

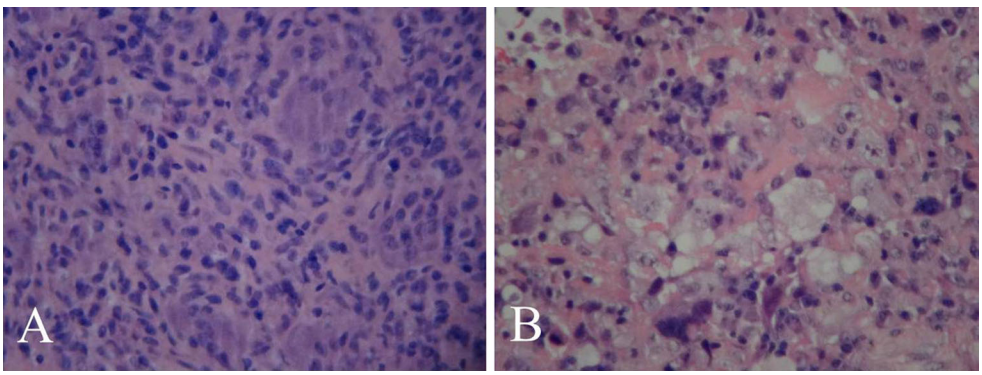

Fig. 2 Pathological images of a patient with SMGCT in the spine who previously received both surgical treatment and radiotherapy (case. #2). **a** The image after first surgery revealed a pathological diagnosis of benign GCT. **b** The image after second surgery indicated a diagnosis of malignant GCT

pain and neurologic deficits, which was common in spine tumors. In our series, MGCT was most likely to infringe upon the thoracic spine. The radiologic features of MGCT were similar to those of conventional GCT: osteolytic lesions, however MGCT showed more aggressive features, with a less distinct margin and more cortical breakthrough.

Histologically, the morphologic features of a classic GCT exists in PMGCT, while residual GCT elements in SMGCT might not be obvious and patient's hospital history needs to be investigated to make the diagnosis [11]. Fibrosarcoma, osteosarcoma, malignant fibrous histiotoma, UPS, and undifferentiated sarcoma were the reported sarcoma types in MGCT with osteosarcoma as the main sarcoma type [23–27]. In our studied, the malignant components included chondrosarcoma, malignant fibrous histiocytoma, osteosarcoma and undifferentiated sarcoma, with osteosarcoma and undifferentiated sarcoma as the main sarcoma types.

Surgical treatment is the foundational treatment strategy for spinal MGCT with the aim of preserving functionality, relieving pain, controlling local recurrence, and promising prolonged survival [20, 30]. Surgical procedures applicable to spine vary from the simplest subtotal resection (curettage) to the most complex total *en bloc* spondylectomy [19]. Although only a limited number of cases were analyzed, it was evident that patients who underwent total *en bloc* spondylectomy had better prognosis when compared to patients with the other two surgical options.

Subtotal resection is a common surgical option in the spine due to its anatomical complexity, but it is confirmed to be insufficient for MGCT in the spine [1, 31, 32]. Piecemeal total resection is considered to be superior to subtotal resection, but it is also associated with a possibility of tumor cell contamination in the surgical field which might cause serious consequences for spinal MGCT. Total *en bloc* spondylectomy is a procedure aimed at surgically removing a tumor in a single, intact piece, fully encased by a continuous shell of healthy tissue (margin) [19]. Anatomical complexity of the spine makes it technically demanding, and careful surgical planning according to the Enneking stage, and WBB system is of great importance [20]. Total *en bloc* spondylectomy is also considered to cause more complications than the other two surgical procedures in the spine, which have been widely discussed in the literature [33–35].

Radiotherapy and chemotherapy were used as adjuvant treatment for MGCT of bone, but their positive effect on recurrence and overall survival remains controversial [7, 32, 36, 37]. With the development of focal irradiation treatment, the recent studies reported the safety and efficacy of radiotherapy in the management of MGCT, but its value is still debated because MGCT is initially thought to be radioresistant and malignant transformation following radiation treatment has occurred [38–40, 43]. Although chemotherapy was considered to be effective in controlling local disease in surgically inaccessible and radioresistant tumors by several reports, a chemotherapeutic protocol for MGCT has not yet been standardized [37, 41]. In our series, postoperative radiotherapy was used in 4 cases, but no significantly positive effect was found. Bisphosphonate treatment which was confirmed to reduce recurrence rate of spinal GCT might provide another adjuvant treatment choice for spinal MGCT.

Distant metastasis is not uncommon in MGCT of bone and the lung serves as the most frequent site [7, 32]. Distant metastasis makes disease control difficult and further threats the survival of patients. Lung metastasis occurred in 4 patients in our series and was thought to be the leading cause of death in these patients.

Preoperative biopsy is needed for surgery protocol formulation, although there is risk of possible nerve damage. However, the diagnosis of PMGCT might initially be missed when a biopsy shows only areas of benign GCT. Intraoperative fast pathological examination which also has a guiding significance for surgery seemed to be more credible in our study.

The prognosis of MGCT is still indefinite due to the rarity of the disease, but the existing cases indicated poor prognosis and short life expectation [36, 42]. Six of the fourteen patients (42.9 %) died in our series with mean survival time of 31 (range 3–64) months. Nascimento et al. and Lihua Gong et al. reported that PMGCT had a better prognosis than SMGCT [11, 29]. Similar outcome was found in our series, all 3 patients with PMGCT were alive with NED, but more than half of patients with SMGCT died.

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Conflicts of interest None.

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