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Research paper

Surgical management and outcomes of spinal clear cell sarcoma: A retrospective study of five cases and literature review

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ABSTRACT

Purpose: Clear cell sarcoma (CCS) is a rare high-grade malignant tumor accounting for less than 1% of all soft tissue sarcomas. CCS in the spine is much rarer and poorly understood. The objective of our study is to discuss clinical characteristics, surgical management and outcomes of spinal CCS.

Methods: Between October 2011 and December 2014, five patients with spinal CCS underwent surgical treatment in our center. Five cases from literature focusing on the spinal CCS were also reviewed. We retrospectively analyzed clinical data and outcome of all ten patients to present our understanding of spinal CCS.

Results: Three en bloc and two piecemeal resections were performed successfully. The syndromes of all the patients were obviously relieved after operation. The mean follow-up period was 24.4 months (range 10–41 months). Two patients died of lung metastasis 10 and 26 months after operation respectively. One patient was alive with tumor recurrence. Other two patients were alive with no evidence of disease at last follow-up.

Conclusions: Prognosis of spinal CCS tend to be worse than CCS in common sites. En bloc resection could be regarded as the first treatment option. Tumor size, tumor location, preoperative neurological status and resection mode might be the potential prognostic factors of spinal CCS.

1. Introduction

Clear cell sarcoma (CCS), a rare high-grade malignant tumor accounting for less than 1% of all soft tissue sarcomas [1], was first described by Enzinger in 1965 [2]. In 1983, CCS was also named malignant melanoma of the soft parts due to its histological similarities to malignant melanoma, such as the presence of melanin, immunohistochemical staining for melanoma-associated S-100 and HMB-45 [3]. With the discovery of chromosome translocation t(12;22) (q13;q12) which leads to the generation of EWSR1-ATF1 fusion gene, clear cell sarcoma was redefined as a distinct type of tumor [4,5].

CCS is often located in the tendons or aponeuroses of the extremities, especially in the foot and ankle [3,6–10]. However, CCS in the spine is extremely rare and poorly understood. Only a few cases specifically focusing on spinal CCS have been reported [11–15]. As a high-grade malignant tumor, CCS is apt to recur and metastasize, with a local recurrence rate of 84% and late metastasis rate of 63% [16]. Radical excision with negative margins is the best option for treating CCS, but it is difficult to achieve in the spine. Here, we retrospectively analyzed clinical data from our patients along with a review of the literature.

2. Materials and methods

A total of five patients with spinal CCS were diagnosed and treated in our institution between October 2011 and December 2014. All the final pathological diagnoses were confirmed by two independent pathologists according to the following histopathological criteria: 1. Tumors were microscopically characterized by a nested to fascicular growth pattern of fusiform tumor cells and/or a diffuse sheetlike fashion of much plumper polygonal or epithelioid cells. 2. In immunohistochemical study, tumors were positivity for S-100, HMB45, MITF, bcl-2, CD57, Melan A etc. 3. The chromosomal translocation t(12;22) (q13;q12) or the resultant fusion gene EWSR1-ATF1 were

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detected by RT-PCR or FISH. [17].

We retrospectively reviewed the hospitalization records, progress notes, surgery information, radiographic images and pathological reports of all patients. This study was approved by the hospital ethics committee and informed consent was obtained from all patients.

Of the five patients analyzed, one (case 4) had been subjected to an incomplete tumor resection in other institution. She was admitted to our center because of tumor recurrence. Other patients were regarded as “intact” cases for they had not received any treatment before admission.

X-ray, computerized tomography (CT) and magnetic resonance imaging (MRI) of the spine were performed in all patients after hospitalization. Tumors were further classified according to the Enneking staging system for all patients and Weinstein-Boriani-Biagini (WBB) classification system for mobile spine based on radiographic findings. Neurologic status was evaluated by Frankel scoring system. One patient obtained her pathological diagnosis after operation in other institution. Three patients received percutaneous needle biopsy in our center. The remaining patient (case 5) refused to have a needle biopsy for fear of possible nerve damage, though we emphasized the significance.

En bloc and piecemeal resections were performed in three and two patients respectively. Patients were followed up at 3, 6, and 12 months after surgery, every 6 months for the next 2 years, and anytime when patients feel uncomfortable. X-ray and/or MRI examination were performed at follow-up. The last status of patients was obtained from office visit or telephone interview.

We also searched the articles related to the spinal CCS using MEDLINE/PubMed as searching engine, and five case reports were reviewed. Then we compared and analyzed both the data in the literature and our own.

3. Results

3.1. Epidemiology and clinical presentation

Our series composed of three men and two women. The age of patients ranged from 20 to 46 years at diagnosis, with a mean age of 27.8 years. The most common symptom was chronic pain, which often radiated to the extremities and could not be relieved by aspirin or acupuncture therapy. Tumor size ranged from 2.4 to 11.9 cm in the maximum diameter, and three of five tumors were larger than 5 cm. Tumor involved posterior elements in two cases, both vertebral body and posterior elements in two cases, and sacrum in one case. Frankel scores were as follows: one patient was Grade C; Grade D and E each were documented in two patients. The clinical data of our patients are listed in Table 1.

3.2. Radiologic studies

The plain radiographs of three patients showed bone destruction. CT scan also demonstrated lytic lesions with irregular soft tissue masses, and inhomogeneous enhancements could be seen after intravenous contrast enhancement. MRI is more sensitive for detecting soft tissue lesions. The tumor lesion was mixed hyperintense on T1WI and hypointense on T2WI, and inhomogeneous enhancement could also be seen on MRI enhancement scan (Fig. 1).

3.3. Treatment

The whole operation process comprised tumor excision, decompression of the spinal cord, reconstruction and stabilization of the spine. Intraoperative frozen section examination was performed in all five cases. Posterior approach was conducted in four patients, while the other one (case 4) whose lesion involved cervical vertebra (zone 1–9 of WBB system) used a combined anterior-posterior approach. En bloc

Table 1
Clinical data of patients with spinal CCS in our institution.

No.	Age (y)/ Sex	Location	Staging*	Symptoms	F-S pre	Resection mode	Tumor size (cm)	F-S post	Adjunctive therapy	Local recurrence/Metastasis	Follow-up (month)	Last status
1	46/M	Sacrum	$G_2T_2M_0$	Radicular pain and dysuria	D	En bloc resection	8.2	D	Bisphosphonate	Local recurrence at 12 months	13	AWD
2	23/M	T10–11	$G_2T_2M_0$ 1–2/A-C	No symptom**	E	En bloc resection	2.4	E	–	–	32	NED
3	26/M	T6–8	$G_2T_2M_0$ 10–12/A-D	Palpable mass	E	En bloc resection	3.8	E	–	–	41	NED
4	20/F	C3–5	$G_2T_2M_1$ 1–9/A-D	Pain and weakness of upper extremities	C	Piecemeal resection	5.3	E	Chemotherapy, radiotherapy and bisphosphonate	Lung and neck lymph nodes metastasis before surgery in our center***	10	Dead
5	24/F	L1–3	$G_2T_2M_0$ 3–8/A-D	Pain and radicular pain	D	Piecemeal resection	11.9	E	Radiotherapy and bisphosphonate	Local recurrence at 18 months; lung metastasis at 24 months	26	Dead

M, male; F, female; F-S, Frankel score; pre, preoperation; post, postoperation; NED, no evidence of disease; AWD, alive with disease; NI, no information.

* Enneking staging was used in all cases, Weinstein-Boriani-Biagini staging was used in mobile spine.

** Tumor was found in health checks.

*** This patient experienced tumor recurrence and metastasis to lung and neck lymph nodes two years after her initial operation in other institution, and she then had an operation of cervical spine tumor in our department due to unrelieved pain and neurologic deficit.

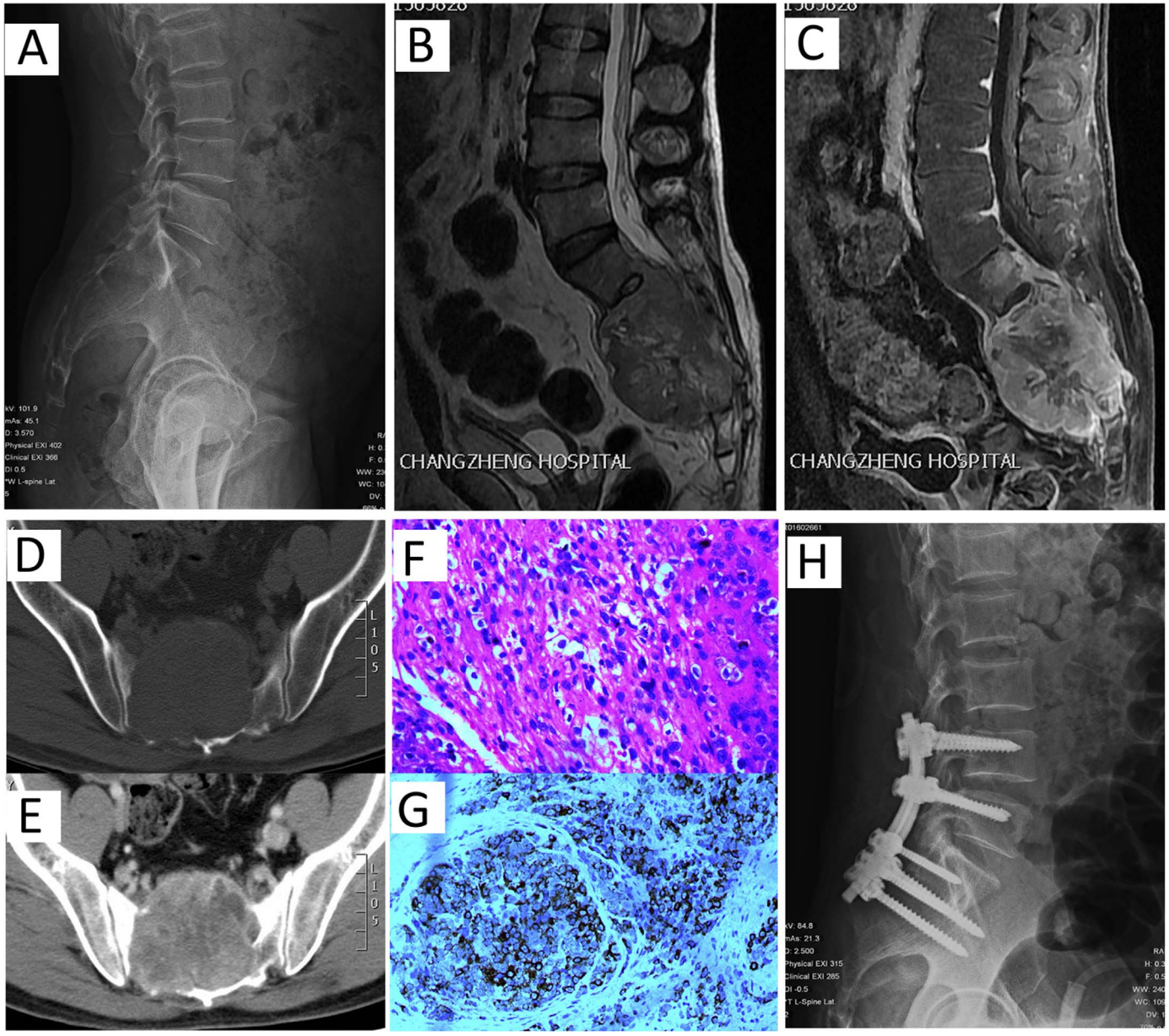

Fig. 1. Images of a 46-year-old man (case 1). (A) The preoperative X-ray showed expansive bone destruction without osteosclerosis or periosteal reaction. (B and C) The preoperative MRI revealed the tumor invaded sacrum and obstructed the spinal canal. The tumor was low signal intensity on T2-weighted image, and inhomogeneous enhancement could be seen on MRI enhancement scan. (D and E) The preoperative CT scans (plain and enhancement) showed lytic lesion with large soft tissue mass and inhomogeneous enhancement. (F) Hematoxylin and eosin (H & E) stain showed tumor cells were polygonal or spindle shaped with rich and transparent cytoplasm and arranged in fascicles and nests separated by fibrous septa. Nuclei were round to oval with predominant nucleoli. (G) Immunohistochemical study demonstrated positive cytoplasmic stainings for HMB-45. (H) The tumor was excised by an en bloc method, pedicle screws, iliac screws and titanium rods were used to reconstruct the stability. Tumor recurrence was found by MRI in other institution 12 months after operation, but the patient refused to provide his MRI films. He rejected a second operation for economic reasons, and was alive with tumor at last telephone follow-up.

resection was performed on three cases (case 1, 2 and 3), other two patients underwent a piecemeal resection. Postoperative pathology examination confirmed two negative margins (case 2 and 3) and one contaminated margin (case 1) for en bloc-resected patients. Intraoperative blood loss ranged from 400 to 6500 mL (mean 2320 mL). All patients recovered well without surgical complication except one (case 4) suffered from cerebrospinal fluid leakage which was resolved by lumbar cistern drainage. Two patients (case 4 and 5) received adjuvant radiotherapy, and chemotherapy was performed on one (case 4) patient. In order to inhibit osteolysis, patients with tumor > 5 cm (case 1, 4, and 5) also received bisphosphonate therapy.

3.4. Follow-up

The mean follow-up duration was 24.4 months (range 10–41 months). Pain and numbness were significantly relieved in all patients after operation. Two patients also experienced an improvement in Frankel scores of 1–2 grades at their 3-month follow up visit. One patient (case 1) experienced tumor recurrence 12 months after operation. We advised him to have a second tumor resection but he refused for economic reasons, and he was alive with tumor at last telephone follow-up. Unfortunately, two patients (case 4 and 5) died of lung metastasis 10 and 26 months after operation respectively.

Table 2
Clinical data of patients with spinal CCS reviewed from literature.

Author/year	Age (y)/Sex	Location	Symptoms	Resection	Tumor size (cm)	Adjunctive therapy	Outcomes/Follow-up (month)
[11]	25/M	Sacrum	Pain and radicular pain	Subtotal resection	11.0	–	Local recurrence at 9 months
[12]	38/M	T5–6	Pain and radicular pain	NI	5.0	chemotherapy	Local recurrence
[13]	41/M	Sacrum	Pain and numbness	Total resection	3.0	–	NED at 6 months
[14]	47/F	C1–2	Altered sensation and Loss of function	Total resection	2.0	–	NI
[15]	18/F	T4–5	Tingling, numbness and pain	NI	6.0	–	NI

M, male; F, female; NED, no evidence of disease; NI, no information.

4. Discussion

Clear cell sarcoma is a rare high-grade malignant sarcoma. It typically affects young adults in their third decades [3], with a mean age ranging from 32 to 41 years [1,3,6,9] and an approximately equal sex distribution [2,18,19]. The most common sites of CCS are extremities. Chung et al. [3] reported 141 cases of CCS, 137 cases of them occurred in extremities. However, CCS in the spine is extremely rare and only a few cases have been described. We presented five cases of spinal CCS in our institution, and also reviewed five cases from literature [11–15] (listed on Table 2). Of all ten patients, the mean age was 30.8 years, and female patients were almost equal to male patients, which may demonstrate that patients with spinal CCS have similar epidemiologic features as patients with CCS in common sites.

Spinal CCS, especially when tumor involves vertebra body or sacrum, is not usually detected in early stage because of the nonspecific clinical manifestations and deep location. As a result, the size of spinal CCS in our series (median 5.3 cm, mean 6.3 cm) is larger than size of CCS in common sites (median 3–4 cm) [1,6,18]. Initially, patients with spinal CCS had no symptoms or felt only a slight back pain. They did not take the slight pain seriously until symptoms became more and more severe. Sometimes when patients sought treatment, the tumor had already been too large to be resected completely. With the growth of the tumor, some of them also complained of radiating pain and neurologic deficit due to spinal cord or root compression.

In order to facilitate surgery protocol formulation, we emphasize the importance of needle biopsy. The radiological imaging of one patient (case 4) hinted that the lesion was a benign neurogenic tumor, and she refused to receive a preoperative biopsy for fear of possible nerve damage. Unfortunately, the following incomplete resection of such a malignant tumor in other hospital leaded to a poor prognosis. Furthermore, melanocytes in CCS, perineural cells, and Schwann cells share a common embryologic origin named neural crest cell [11], which may explain why CCS is easily misdiagnosed as neurogenic tumors. Immunohistochemistry is a good way to distinguish CCS (positive for HMB-45) from neurogenic tumors (negative for HMB-45) [16,20].

Radical surgical resection is the ideal treatment option for CCS. Enzinger et al. [2] reported that patients who underwent a wide resection or amputation had a mean survival of 10 years, while patients who underwent a marginal or intralesional excision had an average survival of 6 years. Hocar et al. [10] summarized that successful treatment was accomplished by complete excision regardless of whether there was an adjuvant therapy. Ferrari et al. [21] proposed that if complete excision had been performed, adjuvant treatment might have been unnecessary. Conversely, In the case of Zhang et al. [11], tumor of the patient recurred nine months after surgery partly because of the residual tumor causing by incomplete resection.

As for spinal CCS, Surgical removal of tumor is also the fundamental treatment strategy [11]. The Spinal operation aims to improve or preserve neurological function, control local recurrence and prolong the survival period [22,23]. En bloc, piecemeal and subtotal resections are the surgical procedures applicable to spine [24]. In view of the potential risk of tumor cell contamination in the surgical field by piecemeal resection, en bloc resection was regarded as the most ideal method for treating spinal tumor. However, en bloc resection is hard to achieve due to the anatomical complexity of spine area, especially when the vital neurovascular structures are enclosed by tumors. In order to achieve relatively good prognosis, three patients underwent an en bloc resection, and we tried our best to remove the tumor as completely as possible by a piecemeal method in other two patients. Only two patients were alive with no evidence of disease at last follow-up, and both of them received an en bloc resection with negative margins. Therefore, facing such a high-grade malignant tumor, we advocate adopting en bloc resection if situation allows. Admittedly, due to the limited number of patients, our tentative idea needs to be proved by further studies.

The effectiveness of preoperative embolization has been confirmed to minimize intraoperative blood loss [25]. Although this intervention may have no benefit to the long-term prognosis of spinal CCS directly, it may also have the potential of ischemic complications [26], yet embolization can play a certain role in making surgery safer and easier. We regretted not performing a preoperative embolization on case 5 who failed to have a more radical surgery partly because of profuse bleeding (6500 mL). Thus we suggest that when tumor is comparatively large and with rich blood supply, preoperative embolization is recommended.

The effectiveness of radiotherapy on CCS is still in dispute. Kuiper et al. [27] approved that adjuvant radiotherapy has a beneficial effect on local control. While Ferrari et al. [21] insisted that radiotherapy was of no benefit for CCS. Meanwhile, the existence of both supporters [7,21,28] and opponents [6,29] makes the role of chemotherapy in CCS also remain controversial. In our series, patients who received adjuvant radiotherapy or chemotherapy failed to achieve a good prognosis. Due to the limited number of patients, we cannot draw the conclusion that whether the adjuvant radiotherapy and chemotherapy are effective in spinal CCS. But considering the side effects, radiotherapy and chemotherapy should be applied cautiously.

Bisphosphonate has been demonstrated to have an inhibitory effect on proliferation and invasion of malignant bone tumors [30]. We used bisphosphonate as an adjuvant treatment in patients with tumor > 5 cm. Novel therapies such as molecular targeted drug: Sunitinib [31], and isolated limb perfusion [32] also has been used in CCS. These therapeutic strategies offer new sights for the treatment of CCS, but further researches are needed.

In comparison with other high-grade malignant tumors, CCS has a relatively good prognosis. 5-year survival ranges from 47–67% [6–10,18], and 10-year survival rate drops to 25–41% [6,8–10,18]. However, in our series the mean follow-up period was 24.4 months, only two of them were disease-free, which may indicate that the prognosis of spinal CCS is worse than CCS in other sites. The reason may be as follows: firstly, due to its deep site and the lack of clinical manifestations in early time, spinal CCS is often diagnosed when the tumor has already involved spinal cord or root and been too large to be resected totally; furthermore, it is the anatomical complexity of spine area that limits the application of radical surgery.

Comparing and analyzing the data of patients who were disease-free (case 2 and 3) with patients who experienced tumor relapse or

metastasis (case 1, 4 and 5), we found that tumor size, tumor location, preoperative neurological status and resection mode could be the potential prognostic factors of spinal CCS. Notably, large tumor size (> 5 cm) has been reported as an independent adverse prognostic factor by many studies [6,8,9]. In our case series and the case reviewed, all of the patients suffered tumor recurrence or metastasis had a tumor no less than 5 cm. Nevertheless, due to the limited number of patients and follow-up time, it is difficult for us to draw conclusions with statistical significance. And we are looking forward to larger and longer researches for this challenging disease.

5. Conclusion

Spinal CCS is an extraordinarily rare tumor and hard to diagnose with poor prognosis. En bloc resection, which is not always possible due to the anatomical complexity of spine area and large tumor size, is the ideal treatment option, while the role of adjuvant treatments is still controversial. Vertebra body or sacrum involvement, large tumor size, poor preoperative neurological status and non-radical resection might be the potential negative prognostic factors of spinal CCS.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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