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ORIGINAL ARTICLE

Percutaneous albumin/doxycycline injection versus open surgery for aneurysmal bone cysts in the mobile spine

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Abstract

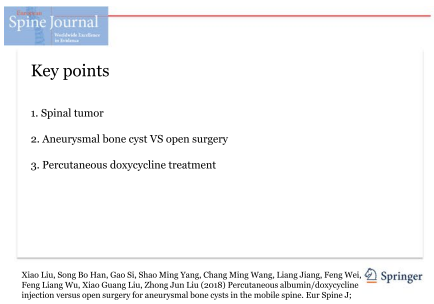
Purpose This study aimed to validate the safety and effectiveness of percutaneous doxycycline/albumin injection for spinal aneurysmal bone cysts (ABCs) as an alternative to open surgery.

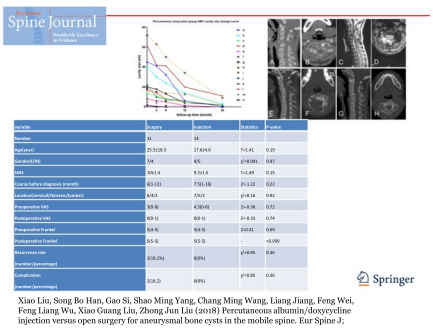
Methods From January 2000 to December 2016, 25 patients who had no/minor neurological deficits (modified Frankel scale D or E) and acceptable local stability (spinal instability neoplastic score < 12) were included in the study, of whom 14 were treated with percutaneous doxycycline/albumin injection (injection group) and 11 were treated with open surgery (surgery group). The demographic and clinical information of the injection and surgery groups were recorded and compared.

Results In the injection group, lesion size was significantly reduced in all 14 patients, all patients showed complete neurological recovery, and 13 patients had complete relief of neck pain; their mean visual analogue scale (VAS) decreased from 3.4 to 0.5. No complication or recurrence was observed during the mean 30.7-month follow-up (range, 24–50 months). In the surgery group, 9 patients had complete neurological recovery and 2 patients had residual slight paresthesia; their mean VAS decreased from 3.4 to 0.5. Two had local recurrence during their follow-up at 66.5 months (range, 50–96 months). Compared with the surgery group, the injection group showed no significant difference in the rate of recurrence ($P = 0.14$) and complication ($P = 0.36$).

Conclusions Percutaneous doxycycline/albumin injection for spinal ABCs can be safely and effectively performed in well-selected cases. It could serve as an alternative treatment, especially for spinal ABCs lesions with acceptable local stability and in patients without severe neurological deficits.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.





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Keywords Spinal tumor · Aneurysmal bone cyst · Percutaneous doxycycline treatment · Open surgery · Recurrence

Introduction

Aneurysmal bone cysts (ABCs) are a relatively rare bone neoplasm with blood-filled spaces separated by connective tissue septa containing fibroblasts, osteoclast-type giant cells, and reactive woven bone [1]. Approximately 10–30% of ABCs involve the spine [2, 3]. They are usually expansive and destructive and can lead to pathological fractures and neurological deficits [4]. Boriani et al. [2] suggested that ABCs are a vascular malformation, and the oncogene *TRE17/USP6* was discovered in ABCs lesions [5, 6].

Treatments for spinal ABCs include open surgery (resection and/or curettage), intracystic injection [7], selective arterial embolization (SAE), and radiotherapy, but surgical treatment is still widely used. Recently, two teams have reported the use of percutaneous doxycycline/albumin injection as treatment for ABCs [8, 9], but its safety and efficiency for potential treatment of spinal ABCs still needs to be verified. This single-center study aimed to determine if percutaneous doxycycline/albumin injection is a safe and effective alternative to open surgery in patients with spinal ABCs.

Methods

We hypothesized that percutaneous doxycycline/albumin injection would be as efficient and safe as open surgery for the treatment of spinal ABCs without obvious local instability and/or severe neurological deficits.

Clinical data

From January 2000 to December 2016, 32 patients were histologically diagnosed with spinal ABCs in our department. Before 2014, open surgery was the standard treatment for all patients with spinal ABCs. Since then, the preferred treatment has been percutaneous doxycycline/albumin injection for patients without obvious local instability (spinal instability neoplastic score [SINS]<12) [10] or severe neurological deficits (muscle strength grade, > 3/5); the choice of open surgery was also introduced to the patients as an alternative method, and finally the informed consent was signed by the patients. Twenty-five patients with spinal ABCs were included, of whom, 14 patients (5 male and 9 female patients; mean age, 17.6 years; range, 10–26 years) were treated with percutaneous doxycycline/albumin injection and 11 patients (4 male and 7 female patients; mean age, 18.4 years; range, 6–36 years) underwent open surgery. Seven patients who underwent open surgery were excluded from this study, because of obvious local instability or severe neurological damage; they were omitted to unify the baseline during comparison.

Imaging and biopsy protocol

The radiological studies routinely included posteroanterior and lateral spinal radiography, bone scan, computed tomography (CT), and magnetic resonance imaging (MRI). The CT raw data of the patient were transferred to an advanced workstation (AW4.5; GE Medical Systems, Milwaukee, WI, USA); then, the contours of the ABCs on each CT slice were manually traced. The cyst volume was calculated using the formula for an atypical ellipsoid [11]. CT-guided biopsy was performed by interventional radiologists to establish a definite diagnosis. After the pathological diagnosis was confirmed, percutaneous doxycycline/albumin injection or open surgery was indicated.

Technique of percutaneous doxycycline/albumin injection

CT-guided percutaneous doxycycline/albumin injection was performed under local anesthesia and intravenous sedation. Intravenous contrast CT was performed to evaluate the blood vessels around the lesion, especially the vertebral artery in the cervical spine. Usually two separate core needles were inserted into the ABCs lesion under CT guidance. The needle size was based on the thickness of the cortical bone overlying the lesion.

A human serum albumin (20%, 5.0 mL) and doxycycline solution (200 mg, 40 mg/mL, 5.0 mL) were agitated 30 times by pumping movements between two connected 10-mL syringes to form a mixture. Then, the mixture was agitated 30 times with air (5.0 mL) to form stable and viscous foam, which is not diluted by blood. During the injection, one needle was used for injection and another for aspiration simultaneously; then, one needle was used for aspiration and another for injection. This process was repeated 3 times. The simultaneous injection and aspiration technique was performed to lower the injection pressure, possibly leading to embolism. This also may minimize the risk of skin burn and neurological irritation secondary to local leakage of doxycycline [8].

Subsequent percutaneous doxycycline/albumin injection was scheduled 3 months after the first injection, unless extensive new bone formation was confirmed by CT. Treatment was considered completed when either lytic areas were

healed with new bone or small lytic areas remained stable after 6 months [8].

Follow-up

The VAS and neurological recovery were recorded. If the patient had recurrent symptoms, immediate MRI and CT were prescribed. X-ray imaging, MRI and CT scanning were performed 3 and 6 months after the index procedure and then every 6 months thereafter. ABCs recurrence was defined as new areas of bony lysis and/or expansion of lucent foci requiring further injection that were detected by CT during the follow-up [8].

Statistical analysis

The differences in age, course of disease, preoperative and postoperative VAS scores (at 12 months), and SINS score between the injection and surgery groups were assessed using the Mann–Whitney U test. Data are presented as median (range) for non-normally distributed data; between-group differences of sex, recurrence rate, and complications were analyzed using the Chi square (χ^2) test. The between-group differences of longitudinal changes between preoperative and postoperative VAS scores and reduction in cavity size of the lesion in the injection group were evaluated using repeated measures. Lesion locations were classified into three categories (cervical, thoracic, and lumbar spine), and their proportions were compared using the χ^2 test between the two groups. A significance threshold of $P < 0.05$ was used for statistical significance. All statistical analyses were performed using SPSS version 20.0 for Windows (IBM Corp., Armonk, NY, USA).

Results

Twenty-five patients had no/minor neurological deficits and had acceptable local stability (SINS < 12), including 14 patients treated with percutaneous doxycycline/albumin injection and 11 with open surgery. The surgery and injection groups were matched in age ($P = 0.19$), sex ($P = 0.97$), SINS ($P = 0.15$), course of disease ($P = 0.22$), lesion location ($P = 0.92$), and preoperative VAS score ($P = 0.72$) (Tables 1, 2).

For the 14 patients in the injection group, 9 lesions were located in the cervical spine (2 of which involved the posterior neural arch adjacent to the vertebral artery), 3 in the thoracic vertebral body, and 2 in the transversus process of the lumbar spine. All patients had experienced local pain for a mean of 6.3 months (range, 0.5–16 months), except 3 patients who were accidentally diagnosed by routine X-ray because of trauma. The mean VAS at presentation was 3.4 (range, 0–7). Three patients had limited range of motion and 4 had neurological deficits, including 1 with C5 radiculopathy and 3 with myelopathy (1 with decreased quadriceps femoris strength of 4/5 and 2 with numbness of the lower limb). The Frankel classification before treatment was E in 10 cases and D in 4 cases (Table 1). The mean pretreatment cystic cavity volume was 24.1 mL (range, 2–74 mL). The mean preoperative SINS was 9.2 (range, 6–11). Four patients had 2 injections, 6 had 3 injections, and 4 had 4

Table 1 General information of the percutaneous doxycycline/albumin injection group

Patient no.	Sex	Age (year)	Lesion site	Preoperative VAS	Preoperative Frankel scale	Preoperative volume* (mL)	Final follow-up volume* (mL)	SINS	No of injection	Complication	Follow-up (month)
1	F	14	T10	0	E	20	No lytic areas	9	4	–	50
2	F	21	C5	1	D	40	No lytic areas	8	4	–	40
3	M	18	C5	3	E	6	0.5	10	3	–	29
4	F	12	T11	5	E	7	No lytic areas	11	3	–	30
5	F	33	C2	0	E	10	0.9	10	2	–	27
6	M	26	L4	7	D	74	0.4	10	4	–	26
7	F	19	C2	5	D	23	0,7	9	3	–	30
8	F	10	C4	0	E	62	No lytic areas	11	4	–	25
9	M	13	C4	3	E	2	No lytic areas	10	2	–	26
10	F	17	T12	6	E	2	No lytic areas	9	2	–	36
11	M	19	L5	6	E	14	0.3	7	3	–	26
12	F	18	C2	7	D	47	No lytic areas	6	2	–	34
13	M	21	C3	3	E	16	No lytic areas	11	3	–	24
14	F	17	C3	1	E	15	0.4	8	3	–	27

F female, *M* male, *VAS* visual analogue score, *SINS* spinal instability neoplastic score

Table 2 General information of patients in surgery group

Patient number	Gender	Age (year)	Lesion site	Preoperative VAS	Preoperative Frankel	SINS	Approach/technic	Follow-up (month)	Complication
1	F	10	C6	8	D	12	En bloc/combined	51	–
2	M	18	C2	5	E	9	Curettage/posterior	84	–
3	M	17	C4	0	D	11	SAE + local resection/posterior	89	–
4	F	6	C5	0	E	9	Curettage/posterior	85	–
5	F	32	T8	0	D	10	SAE + en bloc/combined	53	Paresthesia
6	M	14	C2-3	3	E	8	Curettage/posterior	51	Instrument failure
7	F	18	T2	5	D	12	SAE + local resection/posterior	58	–
8	F	13	C6	0	E	11	Curettage/posterior	50	–
9	F	22	T5	8	E	9	Local resection/posterior	52	–
10	M	16	T6-7	8	E	11	Curettage/posterior	63	–
11	F	36	L1-2	0	E	9	SAE + local resection/posterior	96	Paresthesia

F female, *M* male, *VAS* visual analogue score, *SINS* spinal instability neoplastic score

injections. The cavity volume of the lesions was significantly reduced postoperatively (Table 1 and Figs. 1a–j, 2a–j, 3). All patients returned to full activity, and no recurrence was observed at the last follow-up (average, 30.7 months; range, 24–50 months). Of 14 patients, 13 (92.9%) had complete symptomatic relief and 1 (7.1%) had partial relief with only mild residual neck pain. All 4 patients with Frankel D classification have recovered and regained neurological function. The mean VAS decreased to 0 (range, 0–1). No complications of nerve injury, infection, skin necrosis, or vascular thrombosis were observed.

In the surgery group, 6 lesions were located in the cervical spine, 4 in the thoracic spine, and 1 lesion was present in the lumbar spine. The mean preoperative SINS was 10 (range, 8–12). In 4 patients with myelopathy, 2 complained of burning sensation in the trunk and 2 had slightly decreased in lower limb strength and staggering gait. Two patients underwent intralesional en bloc resection [12],

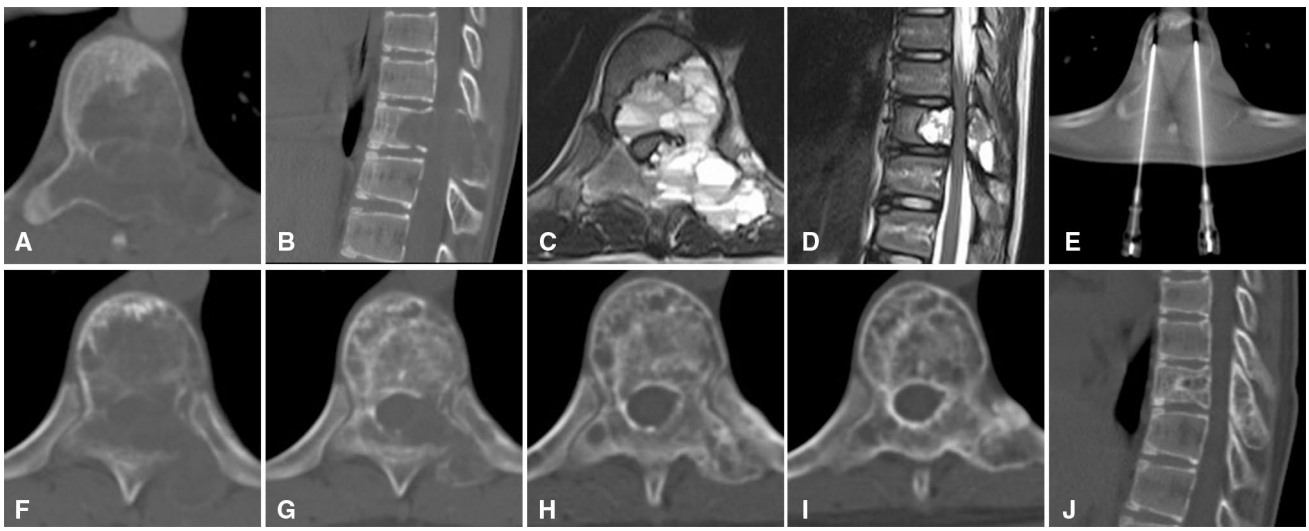

Fig. 1 Representative case of a 14-year-old girl who experienced back pain for 5 months and was diagnosed as having an aneurysmal bone cyst of T10, which was treated with 3 percutaneous doxycycline/albumin injections. **a** and **b** Axial and sagittal CT scans showed an osteolytic lesion involving the vertebral body and neural arch. **c** and **d** Axial and sagittal T2-weighted magnetic resonance imaging scan revealed a polycystic lesion with fluid–fluid levels. **e** Two syringes passing through the pedicles were placed in the lesion within CT-guided trocar. **f** and **g** Axial CT scan before the second and third injections, at 3 and 6 months, respectively, after the first injection. **h** Axial CT scan showing reossification at 9 months after the first injection. **i** and **j** Axial and sagittal CT scans showing further ossification and cavity reduction at the 24-month follow-up

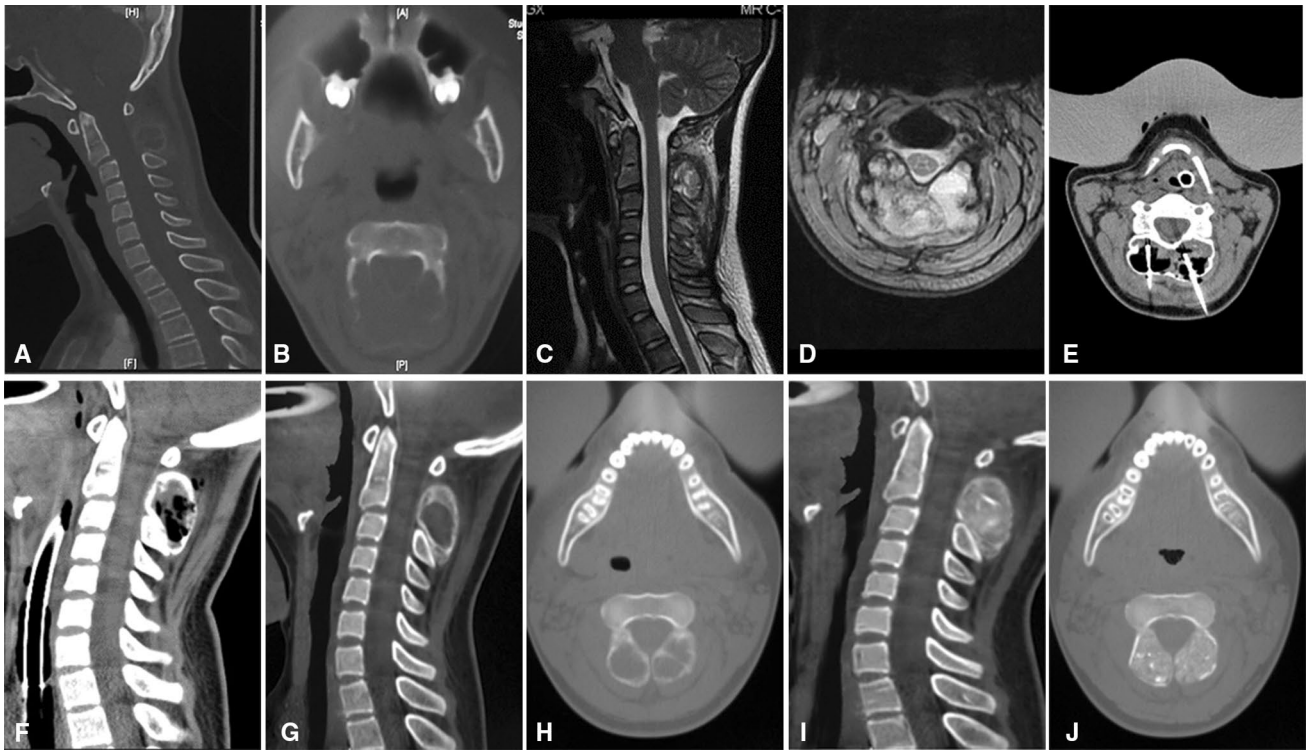

Fig. 2 Representative case of a 18-year-old female experiencing neck pain for 4 months. **a** and **b** CT scans showed an expansive osteolytic lesion of the C2 neural arch. **c** and **d** MRI scans further revealed multiple septa and fluid–fluid levels within the lesion. **e** and **f** It is easier to manipulate when the lesion is located in the neural arch. During the treatment, the mixture was injected into the cystic locules within the neural arch under the guide of CT; then, stable and viscous foams were formed in the lesion. The patient received two injections and the lesion reossified, as seen at the 9-month follow-up examination (**g**, **h**). At 24 months **i** and **j**, complete ossification was observed

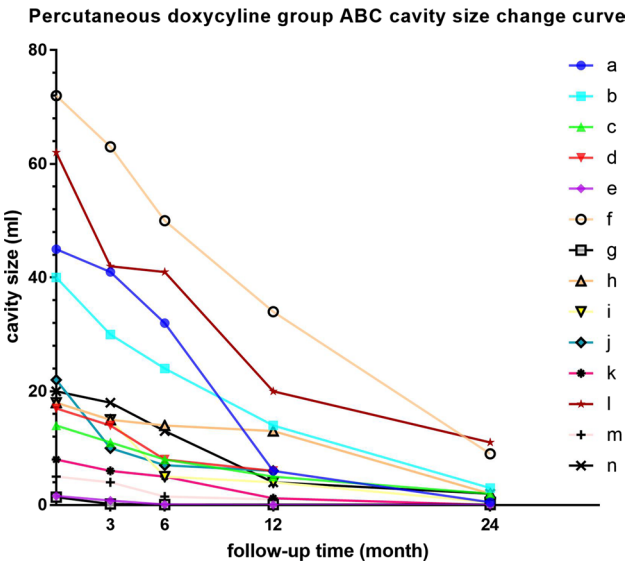

Fig. 3 Change in the ABCs volume after percutaneous doxycycline/albumin injection. *The cyst volume was calculated by the formula for an atypical ellipsoid [9]

4 underwent local resection, and 5 underwent extensive curettage. The mean surgical time was 243 min (range, 76–523 min), and the mean estimated blood loss was 845 mL (range, 100–1600 mL). After the mean 66.5-month follow-up (range, 50–96 months), the mean VAS score decreased from 3.4 to 0.5, 9 patients had complete neurological recovery, and 2 patients had residual slight paresthesia. The median VAS score decreased from 3 (range, 0–8) to 0 (range, 0–1). Two (18.2%) patients who had undergone open surgery experienced local recurrence at the 14- and 16-month follow-up; both underwent revision with resection, fusion, and internal fixation. As for complications, 1 patient had transient neurological deficit. After excluding iatrogenic injury caused by the fixation, the patient was successfully treated by conservative treatment of dehydration and glucocorticoid pulse therapy. The other patient experienced instrument failure, which was treated by revision surgery.

There was no intergroup difference in the rates of recurrence ($P = 0.36$), complication ($P = 0.36$), and decrease in VAS ($P = 0.69$) (Table 3).

Table 3 Comparison of clinical data between surgery and injection group

Variable	Surgery	Injection	Statistics	*P* value
Number	11	14		
Age (year) (Q_{25}, Q_{75})	18.0 (13.8–21)	17.0 (13–22)	$Z=-0.47$	0.64
Gender (F/M)	7/4	9/5	$\chi^2=0.001$	0.97
SINS (Q_{25}, Q_{75})	9.5 (8–10.3)	10 (9–11)	$Z=-1.26$	0.21
Course before diagnosis (month) (Q_{25}, Q_{75})	6 (1–12)	7.5 (1–16)	$Z=-1.22$	0.22
Location (cervical/thoracic/lumbar)	6/4/1	7/5/2	$\chi^2=0.16$	0.92
Preoperative VAS (Q_{25}, Q_{75})	3 (0.75–6)	3 (0–8)	$Z=-0.17$	0.87
Postoperative VAS (Q_{25}, Q_{75})	0 (0–1)	0 (0–1)	$Z=-0.33$	0.74
Preoperative Frankel	5 (4–5)	5 (4–5)	$Z=0.41$	0.69
Postoperative Frankel	5 (5–5)	5 (5–5)	–	>0.999
Recurrence rate (number/percentage)	2 (18.2%)	0 (0%)	$\chi^2=0.85$	0.36
Complication (number/percentage)	2 (18.2)	0 (0%)	$\chi^2=0.85$	0.36

F female, *M* male, *VAS* visual analogue score, *SINS* spinal instability neoplastic score

Discussion

In the present study, we reviewed 25 patients with spinal ABCs treated with open surgery or percutaneous doxycycline/albumin injection to verify whether the latter could be an alternative to open surgery. Our results suggested that percutaneous doxycycline/albumin injection has a comparable treatment outcome to that of open surgery. All the injection procedures were performed successfully without complications or recurrence.

Based on previous literature, the choice of treatment for spinal ABCs is still controversial. Treatment options include surgery (extensive curettage or en bloc excision), embolization (definite treatment or a perioperative procedure), radiotherapy, intralesional injection (doxycycline/albumin or concentrated autologous bone marrow), medication (denosumab), and a combination of these modalities [13, 14]. Each of these treatments has provided successful outcomes, but the complications, technical requirements, learning curve, and treatment costs are different. It is difficult to analyze the efficacy of these treatments because most studies are case reports and most patients receive combination treatments.

In 2013, Shiels and Mayerson [8] first reported the use of percutaneous doxycycline/albumin injection and presented 3 spinal ABCs lesions successfully treated with this technique. Later, Doyle et al. [9] described a patient treated with this method. In this study, 14 patients were successfully treated using this novel technique. However, few studies have focused on the safety and efficacy of percutaneous doxycycline/albumin injection for spinal ABCs.

A proposed mechanism of action for the efficacy of doxycycline was its inhibitory actions on matrix metalloproteinases, angiogenesis, and osteoclasts, all of which contribute to the growth of the lesion [15, 16]. In addition, albumin is a macromolecular biocompatible protein that is an excellent biocarrier for doxycycline [17]. The foam delivery system was derived from the technique of foam sclerosant preparation by Tessari et al. [18]. The foam is more stable and not diluted by blood. Shiels and Mayerson [8] reviewed 20 patients with ABCs (mostly with lesions located in the extremities) who were treated with percutaneous doxycycline/albumin injection; all lesions demonstrated an exact healing response characterized by reduction in lytic destruction and cortical thickening. Similar results were noted in patients with spinal ABCs lesions (Figs. 1, 2).

Some ABCs lesions are contraindicated for SAE due to a feeding artery of limited diameter or an arteriovenous fistula; Boriani et al. [13] reported excellent results with SAE in 17 spinal ABCs, but most lesions were located in the lumbosacral region. For those cases, Barbanti [14] reported 2 cases of concentrated autologous bone marrow injection which were advocated to be a valid treatment. In our study, percutaneous doxycycline/albumin injection could be another alternative.

Surgery is still the most widely used treatment for spinal ABCs, especially for patients with either obvious local instability or severe neurological damage. For most lesions located only in the posterior neural arch, local resection or curettage was performed through posterior approach only. This is always a straightforward method; sometimes, posteriorly located lesions can be handled more easily with the en bloc technique because of the hemorrhagic nature of ABCs, and intralesional excisions possibly confound with profuse intraoperative bleeding. Shibuya [19] also suggested the possibility of less invasive surgical approach by reporting a case of L3 ABCs treated with percutaneous endoscopic lumbar discectomy (PELD). For complex cases such as C1–C2 lesions and lesions invading both the posterior elements and the vertebral body/vertebral artery (especially for the Enneking S3 lesions), total spondylectomy was considered. This method, however, is accompanied with relatively more

blood loss and complications due to extensive manipulation of surrounding normal tissue even if the recurrence rate is lower. Similar to the results of previous research, all patients in this study who underwent surgical resection demonstrated improved neurological function and alleviation of local pain, as shown by the decrease in the VAS score. Although surgical resection had an acceptable rate of local control, which was approximately 90% in large series [20–22], ABCs have a recurrence rate between 12% and 71% without en bloc resection [23]. In this study, 2 (18.2%) patients in the surgery group experienced recurrence, whereas no patient in the injection group experienced recurrence. There was no between-group difference in the rates of recurrence, and this is possibly due to the small sample size. For patients with obvious local instability or severe neurological impairment, open surgery is always the first option because rapid reconstruction of local stability and decompression are the overriding goals.

This study had several limitations. First, because the disease is rare, the sample size of the study was small. This retrospective data set is susceptible to confounding, which is typical in retrospective studies. A future multicenter, prospective study with a larger sample size is needed to formally evaluate interobserver measurement variation and more detailed descriptions of radiographic changes during ABCs healing after doxycycline injection treatments. Additionally, a larger sample size will allow for comparison between the injection treatment and multiple other methods including SAE, radiotherapy, and RANK-ligand inhibitors such as denosumab. Second, percutaneous doxycycline/albumin injection is a relatively new treatment started from 2014 in our institution; the patients in the injection group have a shorter follow-up duration than that of the surgery group. Although the mean 30.7-month follow-up the injection group was longer enough to capture more than 90% of potential recurrence ranging from 18 to 24 months [24–26], Hauschild [27] suggested continuous clinical and radiological follow-up for years following initial treatment and lifelong in cases treated with radiotherapy. Thus, a further five-year follow-up was needed to determine whether the ABCs will ultimately recur.

Conclusions

Percutaneous doxycycline/albumin injection for spinal ABCs can be safely and effectively performed in well-selected cases. It could serve as an alternative treatment, especially for ABCs lesions in the mobile spine with acceptable local stability and in patients without severe neurological deficits. Future studies can present more findings on the efficacy and safety of percutaneous doxycycline/albumin injection for many patients with spinal ABCs.

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Compliance with ethical standards

Conflict of interest Xiao Liu, Song Bo Han, Gao Si, Shao Ming Yang, Chang Ming Wang, Liang Jiang, Feng Wei, Feng Liang Wu, Xiao Guang Liu, Zhong Jun Liu declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. “For this type of study, formal consent is not required”.

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