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Original Article

Aneurysmal bone cyst secondary to giant cell tumor of the extremities: a case series of 30 patients

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Abstract: The purpose was to investigate the clinical features, diagnosis, treatment, and prognosis of aneurysmal bone cyst (ABC) secondary to giant cell tumors (GCT) of the extremities. Data from patients with ABC secondary to GCT of the extremities were obtained from the medical records. Clinical features, imaging findings, pathologic diagnosis, surgical methods, and prognosis were analyzed. The median age of the patients was 33 years (range 15 to 52 years) and 83.3 percent were between 20 to 40 years. The lesions were mainly located in the proximal tibia and distal femur, accounting for 63.3% (19/30). 21 patients were treated with curettage, and 9 with tumor resection. The recurrence rates of the curettage group and resection group were 52.4% and 11.1% respectively. However, the average postoperative (Musculoskeletal Tumor Society) MSTS score were 28.6±1.2 post-curettage, and 25.0±0.5 post-resection, with a significant difference between the 2 groups ($P<0.01$). In these relapsed patients, 10 underwent a second curettage, while 2 cases underwent a resection and there was no postoperative re-recurrence in both groups. A comprehensive analysis should be performed when making the diagnosis of ABC secondary to GCT. Although the recurrence rate is higher, curettage is still the optimal method for satisfactory joint function. If recurrence occurs after the first curettage, a second curettage should be performed.

Keywords: Giant cell tumor, secondary aneurysmal bone cyst, extremities

Introduction

Giant cell tumor (GCT) is a benign lesion, but has a high tendency for recurrenceand invasion [1]. GCT is more likely to occur in patients between 20-40 years of age. Common locations of GCT are around knee, including the proximal tibia and distal femur [2]. Aneurysmal bone cyst (ABC) is made up of several cystic cavities which contain uncongealable blood. The individual cystic cavities are separated by septa, which are composed of fibrous tissues, blood capillaries and giant cells [3, 4]. Aneurysmal bone cysts are usually located in long bones including proximal tibia, distal femur, and proximal humerus. Unlike GCT, ABCs always invade the epiphyseal ends of long bones. Also, the most frequent age for ABC is 10-20 years [5, 6]. However, the pathogenesis of ABC arising from GCT remains unclear. Some scholars believe that the growth of the GCT causes an internal vascular disorder and arteriovenous fistula formation. The hemodynamic changes caused by the fistula lead to vasodilation and bone destruction, resulting in the formation of ABC [7]. Others believe that internal hemorrhaging of GCT may lead to reactive hyperplasia of the bone, and the formation of ABC [8].

Intralesional curettage and tumor resection are the primary treatment methods for ABC secondary to GCT. Whether the secondary ABCs affect the treatment outcome and postoperative recurrence of GCTs remains controversial among surgeons. Some scholars believe that the presence of secondary ABC has little effect on the surgical outcomes [9]. However, others believe that secondary aneurysmal bone cysts may significantly increase the amount of intraoperative bleeding, and increase the surgical

difficulty of GCTs as compared to simple GCTs [10].

As far as we know, there are few reports specializing in ABC secondary to GCT. However, the diagnosis and treatment of the disease remain challenging. This study retrospectively analyzed 30 patients with ABC secondary to GCT, diagnosed and treated at our institution. The clinical features, imaging findings, histopathologic findings, surgical methods, and prognosis of each case were analyzed and summarized to provide complete clinical information.

Materials and methods

Clinical Information

This is an observational study. The study protocol was approved by the Medical Ethics Committee of the First Affiliated Hospital of Guangxi Medical University, Approval number: 2019 (KY-E-090). Between January 2010 and June 2016, a total of 30 cases of ABC secondary to GCT were retrospectively enrolled in this study. The inclusion criteria: (1) There was a post-operative pathologic confirmation of ABC secondary to GCT; (2) Patient data including diagnosis, treatment, and follow-up are complete. The exclusion criteria: (1) Single GCT or ABC; (2) Recurrent lesions; (3) Patients who refused surgery; (4) Lesions located other than in an extremity; (5) Patients with incomplete follow-up data.

Preoperative diagnosis

All patients underwent preoperative X-ray scans of the affected limbs. 25 underwent an additional CT scan while 7 underwent MRI. Preoperative biopsy was performed in 10 of the analyzed cases. Among all cases, 6 were diagnosed with ABC secondary to GCT, 3 with simple GCT, and 1 with primary ABC.

Surgical method

Of these patients, 21 underwent intralesional curettage and 9 underwent en-bloc tumor resection. Curettage was usually used in patients with small tumor volume, no articular surface invasion or a soft tissue mass. Otherwise, surgical resection was performed, which involves the use of a bone chisel to open the outer cyst wall following exposure. Different sizes of curettes were then used to quickly scrape out the tumor tissue. In case of excessive hemorrhage, gauze may have been used for temporal hemostasis until the bleeding point(s) are located and successfully electrocoagulated. Finally, the residual cavity was filled with bone cement, autografted bone or allogenic bone. En-bloc resection was aimed at complete elimination of the tumor with little regard to function, in order to limit the chances of recurrence. The reconstruction requirements post en-bloc varied according to the location of the primary lesion. Artificial joint reconstruction, free fibular grafts for the distal radius, or no reconstruction (in the case of fibula tumors) may have been employed.

Statistical methods

The chi-square test and Fisher's exact test were used to assess different rates between groups. The difference between two independent samples was statistically analyzed using the Mann-Whitney U test for non-parametric analysis. Statistical significance was defined as $P<0.05$. All analyses were performed with IBM SPSS (version 22.0).

Follow-up

The patients were followed up through outpatient service and telephone consultation during the first year postoperative, and follow-up was scheduled every 3 months. It was then scheduled once every 6 months during the second year postoperative after which it was once annually from the second to the fifth years. Affected limbs were scored according to the Musculoskeletal Tumor Society Score (MSTS) [11].

Results

Clinical features

There were 18 men and 12 women with an average age of 33 years (range 15-52 years). There were 2 cases in the 15-20 year range, 25 cases in the 20-40 year range, and 3 cases over the age of 40 years. The tumor locations were mostly around the knee joint: 11 of the cases were located in the distal femur, 8 in the proximal tibia, 3 in the proximal humerus, 2 cases each located in the distal radius and calcaneus, and 1 case in the proximal fibula. According to the Campanacci grading, there were 4 cases of Campanacci grade I, 6 Cam-

Table 1. Data of patients with aneurysmal bone cyst secondary to giant cell tumor

No.	Age (years)	Sex	Medical history (month)	BMI (kg/m^2)	Location	Campanacci grade	Surgical method	Bone cement	Recurrence	Relapse time (months)
1	30	M	2	24.7	Distal femur	3	Curettage	Y	Y	1
2	41	M	1	25.6	Distal femur	3	Curettage	Y	Y	6
3	32	M	7	23.1	Proximal tibia	3	Curettage	Y	N	/
4	43	F	5	26.8	Distal femur	1	Curettage	Y	Y	6
5	46	F	4	27.2	Distal femur	3	Curettage	Y	Y	2
6	36	M	5	26.4	Proximal tibia	3	Curettage	Y	N	/
7	33	M	2	25.7	Proximal femur	2	Curettage	Y	N	/
8	15	M	4	18.3	Proximal femur	1	Curettage	Y	N	/
9	26	M	5	23.5	Proximal humerus	3	Curettage	Y	N	/
10	43	M	11	21.0	Proximal tibia	3	Curettage	Y	Y	2
11	24	M	2	22.8	Distal femur	2	Curettage	N	Y	2
12	25	F	4	20.7	Distal femur	1	Curettage	N	Y	1
13	42	M	9	26.6	Proximal tibia	3	Resection	/	N	/
14	34	F	4	23.4	Proximal tibia	3	Curettage	N	Y	12
15	36	M	15	22.8	Calcaneus	3	Curettage	Y	N	/
16	27	F	5	24.2	Distal radius	2	Curettage	N	N	/
17	35	F	8	23.9	Dibula	3	Resection	/	Y	14
18	31	M	2	22.4	Proximal tibia	3	Resection	/	N	/
19	52	F	9	27.3	Distal radius	3	Resection	/	N	/
20	29	F	10	18.4	Proximal humerus	3	Curettage	N	Y	24
21	38	M	7	24.3	Calcaneus	2	Curettage	Y	N	/
22	26	F	4	20.8	Proximal humerus	3	Curettage	N	N	/
23	38	M	8	26.2	Distal femur	1	Curettage	N	Y	20
24	25	M	7	19.9	Proximal humerus	2	Resection	/	N	/
25	30	F	4	21.7	Distal femur	3	Resection	/	N	/
26	30	M	3	24.5	Proximal tibia	3	Resection	/	N	/
27	34	F	3	24.4	Proximal tibia	3	Curettage	Y	Y	1
28	24	F	2	18.5	Distal femur	2	Curettage	Y	N	/
29	36	M	3	25.9	Proximal tibia	1	Curettage	Y	N	/
30	29	M	5	21.6	Distal femur	3	Curettage	Y	N	/

panacci grade II cases, and 20 Campanacci grade III cases. All 30 patients reported local symptoms, of whom 12 had obvious local masses (**Table 1**).

Preoperative imaging and biopsy

The preoperative X-ray and CT scan of the secondary ABC showed an eccentric and expansile bone lesion. When the patient's condition was serious, cortical destruction by a soft mass was observed (**Figure 1A**, **1B**). CT findings provided more clarity in distinguishing between a solid GCT lesion and a cystic secondary ABC lesion (**Figure 2A**), and some characteristic changes such as intralesional sclerosing (**Figure 3A**), wide indentations, and bone ridges (**Figure 3B**) were clearly seen. In this study, there were 7 cases with obvious wide indentations, 5 cases with intralesional sclerosis, and 3 cases with intralesional calcification (**Figure 3B**). On MRI, ABC lesions were characterized by enlarged masses with lobulated outer margins. The lesions were also found to have low signal intervals on both T1WI and T2WI. The fluid in the cystic cavity showed uneven low or medium-high signal on T1WI sequence and an uneven high signal on T2WI (**Figure 1C**). On enhanced scans, the scanning interval within the capsule and capsular wall were generally

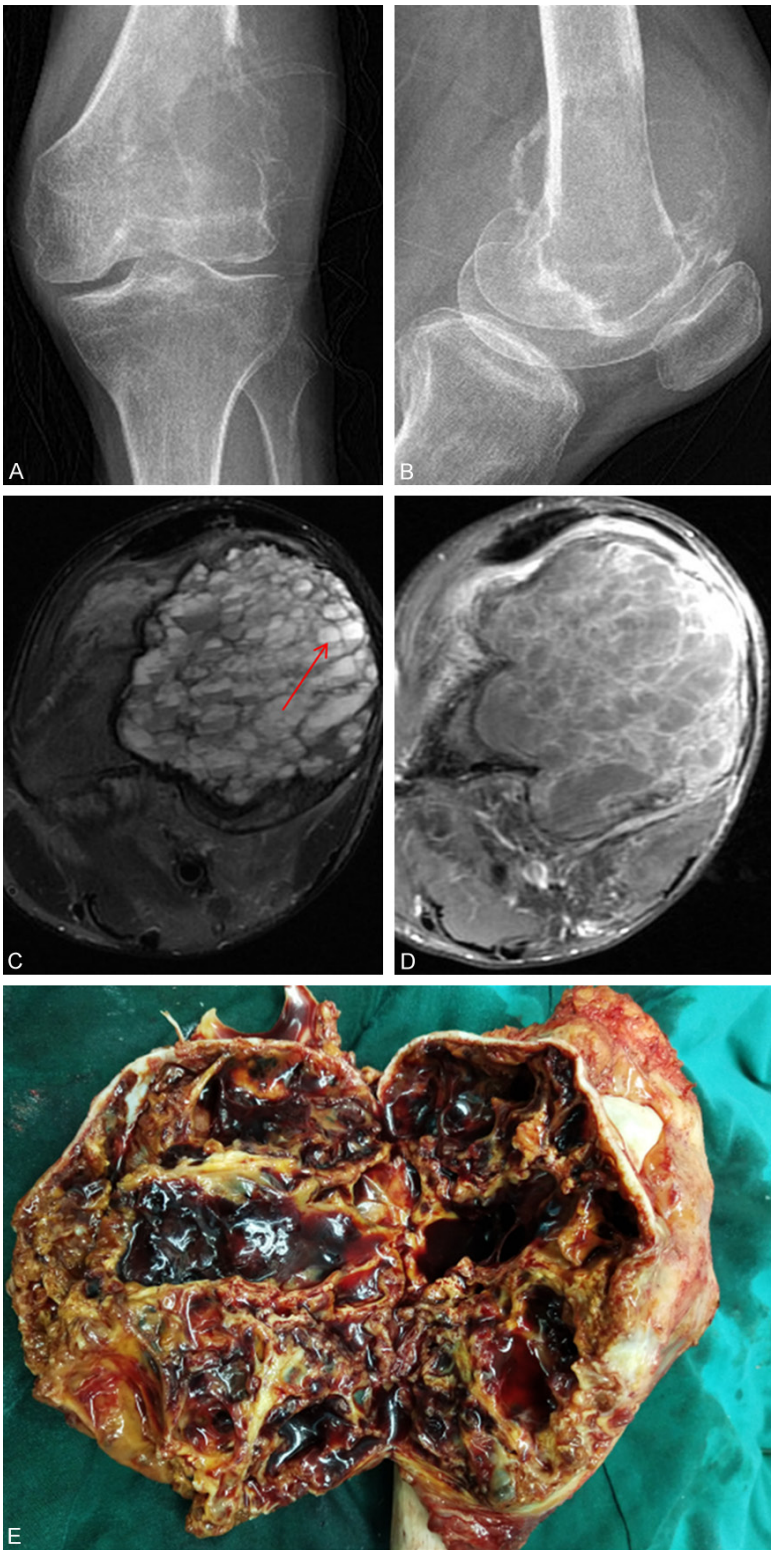

Figure 1. A case of ABC secondary to giant cell tumor located in the distal femur. A, B. X-ray showed multiloculated osteolytic cortical destruction with a soft tissue mass; C. T2WI transverse section of MRI exhibited fluid-fluid interface (Red arrow); D. T1WI transverse section of enhanced MRI revealed interval within the capsule and the capsular wall are generally improved; however, the cystic part does not show any obvious enhancement; E. Internal anatomy of the secondary ABC shows multi-lobulated cystic architecture containing a mixture of coagulated and uncoagulated blood.

improved; however, the cystic part did not show any obvious improvement (**Figure 1D**). Among the cases reviewed for this study, 5 underwent preoperative MRI scans, with 2 of them showing obvious fluid-fluid levels.

Preoperative biopsy was performed in 10 of the cases reviewed, and only 6 among them were consistent with postoperative pathology. Three of the reviewed cases were misdiagnosed as simple GCT, while 1 was misdiagnosed as primary ABC.

Preoperative diagnosis

According to the preoperative clinical manifestations, imaging findings, and histopathologic findings, 21 of the 30 reviewed cases were diagnosed as secondary ABC, 6 cases as simple GCT of bone, and 3 cases as primary ABC.

Follow-up

Curettage was generally used for small tumor volumes, with no invasion of the articular surface and no soft tissue mass formation. Otherwise, resection was performed. Among the 30 reviewed cases, 21 underwent intralesional curettage while 9 underwent surgical resection. The average amount of intraoperative blood loss during intralesional curettage was 404 ml (range 150-500 ml), while the average blood loss by resection was 270 ml (range 100-430 ml).

Recurrence occurred in 11 post-curettage cases (recurrence rate 52.4%), and 1 in resection case (recurrence rate 11.1%). The difference between the two groups was significant (P=0.049). The recur-

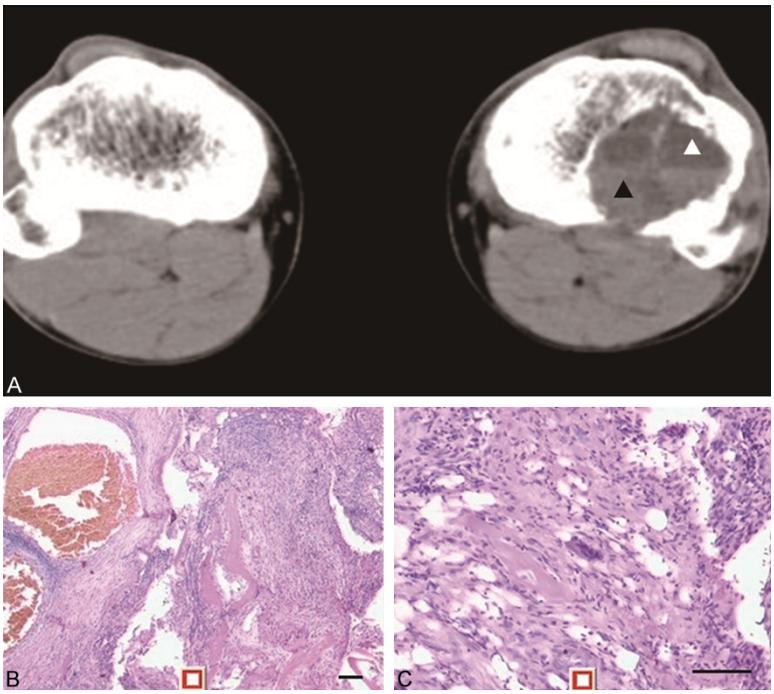

Figure 2. A case of secondary ABC associated with a giant cell tumor of the proximal tibia. A. The solid GCT lesion (black triangle) and the cystic secondary ABC lesion (white triangle) can be easily distinguished on computerized tomographic (CT); B, C. Postoperative pathology showed that the solid part of the lesion was composed of mononuclear stromal cells with scattered multinucleated giant cells. Bar =100 μm, H&E stain, 10×40 and 10×100.

rence rate was 42.9% (six of fourteen) in patients using bone cement and 71.4% (five of seven) in patients without bone cement; the difference was not significant (P=0.361). The time to recurrence ranged from 1 to 24 months postoperatively with a mean of 7.6 months. The average postoperative MSTS scores were 28.6±1.2 post-curettage, and 25.0±0.5 post-resection, with a significant difference between the 2 groups (P<0.01). 10 of the relapsed cases underwent a second curettage, while one case underwent a resection and the other one underwent a second resection. There was no postoperative recurrence in either case.

Postoperative pathologic findings

All patients with ABC secondary to GCT were pathologically confirmed after surgery. Gross analysis of the pathologicspecimens showed obvious cystic expansion and dilatation of the bones; the cortical bone was thin with varying degrees of damage to its integrity. The internal anatomy of the secondary ABC showed a multi-lobulated cystic architecture containing a mixture of coagulated and uncoagulated blood (**Figure 1E**). Under microscopy, mononuclear stromal cells with several diffuse multinucleated giant cells were observed, and the nuclear sizes of the multinucleated giant cells were similar to those of the stromal cells, which demonstrated the presence of GCT. Also, the typical structure of aneurysmal bone cyst was perceived next to the GCT. These structures appeared as a group of blood-filled cavities separated by septa containing stromal spindle cells, fibroblasts, bone trabeculae, histiocytes, hemosiderin-filled macrophages, capillaries, and giant cells (osteoclasts) (**Figure 2B**, **2C**).

Discussion

Many studies have focused on simply GCT or ABC [12], but there are few reports concerning ABC secondary to GCT of the extremities, and this has caused some misdiagnosis of the disease to many clinicians. Additionally, whether secondary ABC affects the therapeutic outcome of GCT remains controversial.

The results of this study show that the clinical features of ABC secondary to GCT are different from those of primary ABC, but similar to those of simple GCT. Primary ABC occurs mostly in adolescents, with 80% of cases occurring in patients less than 20 years [13, 14], while simple GCT occurs mostly between the ages of 20-40 years. The age of patients can therefore be used for differential diagnosis. In cases with onset between 20 to 40 years, simple GCT or ABC secondary to GCT may be considered. In this study, ABC secondary to GCT was mostly located in the epiphyseal ends of the long bones, while primary ABC was located in the epiphysis and diaphysis of the involved long bones (2). Hence, the location of ABC may also be an important indicator of the differentiation.

Radiography is essential for the diagnosis of ABC secondary to GCT. X-ray examination is the preferred choice for simple GCT diagnosis since

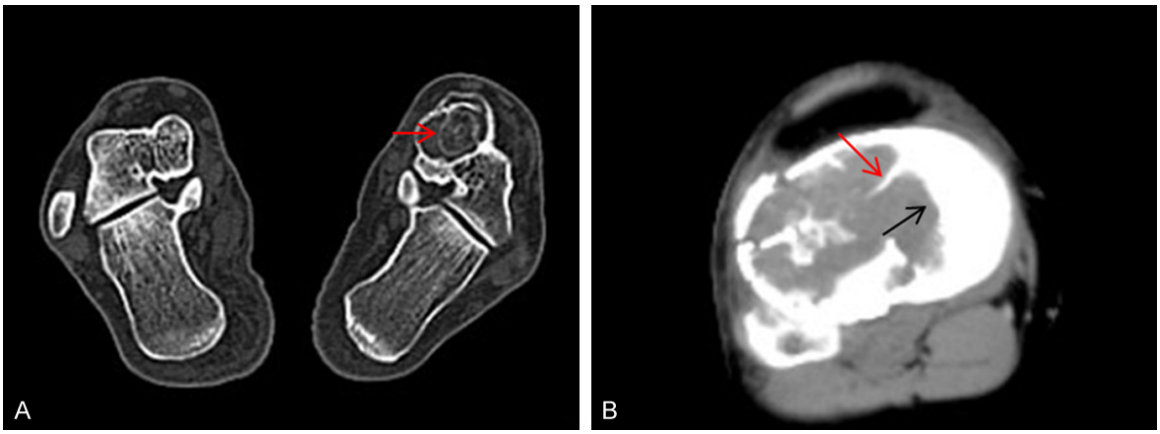

Figure 3. The CT of two patients diagnosed with ABC secondary to giant cell tumor showed some characteristic changes. A. Sclerotic rim; B. Wide indentations (Black arrow) and bone ridges (Red arrow).

it is relatively cheap and easily available in hospitals and clinics. X-ray can be used to identify the lesion as a low density area with different degrees of swelling. It can also detect cortical integrity and whether or not there is a pathological fracture. However, X-ray has low specificity and limited diagnostic value in distinguishing ABC from secondary or primary ABC of GCT. Therefore, CT or MRI is often needed to aid further diagnosis [15]. In this study, none of the cases was diagnosed exclusively using X-ray. On CT, the lesions are much clearer, and are characterized as a cystic mass with thin wall and either intact or incomplete cortical bone shell [16]. Primary solid lesions and secondary cystic foci can be also distinguished on CT, which is an important basis for diagnosis of ABC secondary to GCT. (**Figure 2A**). At the same time, the presence of wide indentations and bone ridges (**Figure 3B**) can suggest the possibility of a secondary ABC. Outward pressure exerted by the rapidly expanding secondary ABC causes a wide indentation and the development of bone ridges [17]; these changes are usually absent in simple GCT cases. The presence of calcified shadows in the lesion and sclerosing edges could also suggest that the lesion is ABC secondary to GCT (**Figure 3A**), since such changes are also absent in simple GCT [16, 18]. In this study, 7 of the cases reviewed had signs of wide indentations, 3 had signs of intralesional calcifications, and 5 cases had signs of sclerosing edges. MRI produces better resolution images of fluid and soft tissue changes in both the primary and secondary lesions. In some cases, a typical fluid-fluid level (**Figure 1C**), formed by blood accumulation in the cyst cavity could be seen. This is suggestive of ABC secondary to GCT, as such changes are usually absent in primary GCT. Enhanced MRI scans provide obvious enhancement of the GCT as well as the edges of the secondary ABC. However, there were no internal enhancements in the cysts. Hence, these different enhancement features can be used to distinguish between simple GCT and ABC secondary to GCT (**Figure 1D**).

Preoperative biopsy is of significant value for the definitive diagnosis of ABC secondary GCT. However, because the puncture samples obtained for biopsies are limited in scope, some primary or secondary lesions may be misdiagnosed [19]. Among the 10 cases who underwent preoperative biopsies, 6 were consistent with their postoperative histopathologic findings, while 3 were postoperatively found to have been misdiagnosed as simple GCT and 1 as primary ABC. Therefore, a combination of clinical features, imaging findings, and preoperative biopsy findings is necessary for the definitive preoperative diagnosis of secondary ABC. To confirm the diagnosis of ABC secondary GCT, both structures of these two diseases should be observed microscopically. The pathologic characteristics of GCT include multinucleated giant cells and some round or oval stromal cells. The nuclei of the multinucleated giant cells were similar in size to those of the stromal cells. Concurrently, cystic structures filled with blood cells often appear next to GCT structures. Also, septa containing reactive osteoid material with osseous trabeculae, lined with plump osteoblasts were observed in the

lesion. The impact of secondary ABC on the treatment of GCT remains controversial. Some scholars believe that secondary ABC has no significant impact on the efficacy of GCT treatment [19, 20]; however, these studies were mostly case reports with limited follow-up periods. In this study, the recurrence rate following intralesional curettage was 52.4%, which is significantly higher than the currently reported recurrence rate for simple GCT (10%-20%) [21-23]. Therefore, this shows that the secondary ABC may have increased intraoperative bleeding, blurred the field of vision, and increased the difficulty of complete removal of the lesion, eventually leading to the high recurrence rate. To control the intraoperative excessive hemorrhage, gauze packing can be used until the individual bleeding points are successfully stopped. Close attention should also be paid to postoperative follow-up and treatment planned if recurrence is suspected. In this study, there were a total of 12 recurrences following surgical treatment. Ten of the relapsed cases underwent a second curettage, while 2 cases underwent a resection. There was no postoperative recurrence in either case. We therefore believe that in case of postoperative recurrence of ABC secondary to GCT, a second curettage could be performed for its lower re-recurrence rate and better postoperative function of the limb.

Previous studies have reported that the recurrence rate after surgical resection is low, but the function of the affected limb and postoperative quality of life are significantly reduced. The recurrence rate following intralesional curettage is high, but the limb function is usually affected to a limited degree, making it the surgical choice for most surgeons and patients [24-27]. The recurrence rate in this study after curettage was significantly higher than that after surgical resection (52.4% vs. 11.1%, $P< 0.05$). However, the follow-up MSTS scores were better in the post-curettage cases than in the post-resection cases (28.6 vs. 25.0, $P< 0.01$). There was no significant difference in recurrence between the two groups (37.5% vs. 71.4%, $P=0.193$), which could be attributed to the small sample size. Other adjuvant therapies, such as liquid nitrogen, phenol, or argon, were not used for uncertain efficacy and possible side effects according to studies [21, 22]. Many authors suggested that the surgical standard treatment should be extensive curettage followed by using the burr [26, 27]. However, all patients included in our study were selected from January 2012 and June 2016, during which time the burr had not yet been applied in our hospital. However, we still believe that if a burr is available curative effect is good. Based on these findings, we hold that simple curettage is best for GCT with integrity of bone cortex, while extensive curettage should be used in lesions with high recurrent risk, such as when combined with ABC. Additionally, when the tumor breaks through the cortex or even combines with a soft mass, en-bloc resection should be performed.

There are several limitations to our study. First, the sample size involved in this study was insufficient. Second, we did not include some patients with ABC or GCT patients as controls. Also, this was a retrospective study. Therefore, prospective research with a larger sample size is necessary.

Conclusion

A comprehensive analysis should be performed during the diagnosis of ABC secondary to GCT. Intralesional curettage should be done as first choice of treatment and if recurrence occurs, a second curettage can be performed.

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Disclosure of conflict of interest

None.

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