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ORIGINAL STUDY

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Treatment of bone cysts by percutaneous injection of demineralized bone matrix mixed with bone marrow

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Bone cysts whether aneurysmal or simple, are known for their tendency to recur. To replace the classical aggressive surgeries, minimally invasive techniques were developed giving differing results based on variable radiographic criteria. No unique percutaneous treatment has proven effective on both types of cysts. The purpose of this study was to evaluate with volumetric MRI calculations the benefit of percutaneous injection of demineralized bone matrix mixed with autogenous bone marrow on both types of cysts. Twenty-seven cysts; 6 aggressive aneurysmal bone cysts (ABCs) and 21 active simple bone cysts (SBCs) were treated with our percutaneous treatment in this case series. Regular MRIs were performed to calculate their volumetric evolution starting before treatment and with a minimal two-year follow-up. A cyst was considered healed when its final residual volume shrank to less than 50%. To allow statistical comparison between both types of cysts, 13 previously reported ABCs treated with the same protocol in our institution were joined to the 6 present ABCs. Four ABCs healed with a single injection while the 2 others recurred. Five SBCs healed with a single injection, 9 others after a second injection and 2 others after a third injection. Five SBCs were considered non-healed. The present healing rate in 67% of ABCs is consistent with the previous series as there was no significant difference (p=0.37). The better global healing rate for ABC (79%) was not statistically different from the SBC healing rate (76%) (p=0.83). The percutaneous injection of demineralized bone matrix mixed with bone marrow is an effective treatment for both types of cysts.

Keywords: Aneurysmal bone cyst; demineralized bone matrix; MRI; simple bone cyst.

INTRODUCTION

Aneurysmal bone cysts (ABCs) present with an estimated prevalence of 1.4 cases per 100,000 individuals *(1)* and occur mainly in young people aged between 6 and 20 years. Symptoms are local pain, tenderness, and swelling. Most ABCs are multiloculated and contain blood fluid. ABCs can be primary or secondary to another tumor (benign or occasionally malignant).

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Simple bone cysts (SBCs) are more common. Each year, incidence is estimated at around 1 per 10,000 children aged from 5 to 15 years *(2,3)*. SBC content is serous. This cyst usually remains asymptomatic until the inaugural pathological fracture. SBCs tend to naturally consolidate once the patient reaches skeletal maturity but may induce multiple fractures and limb length discrepancy.

To treat these bone lesions, two main approaches have been used: either open curettage or minimally invasive techniques. The first approach hypothesizes that consolidation requires cyst removal. The second opposite approach theorizes that walls and septa cells can participate in the healing process. Aggressive surgery is associated with increased morbidity without guarantee of increased success: recurrence rate reaches 7% to 31% in ABCs *(4)* and 35% to 45% in SBCs *(5-9)*.

As a reaction to the failure and morbidity of aggressive surgery in those furthermore benign lesions, a variety of minimally invasive techniques were developed. Those treatments show differing rates of success based on variable radiographic criteria going from a simple sclerosis of the cyst to the Modified Neer Outcome Rating System (see related articles in the Discussion paragraph). Most failures occur within the 2 first years.

We have developed and previously published a percutaneous injection of autologous bone marrow (ABM) mixed with demineralized bone matrix (DBM) for the treatment of ABCs in 13 patients *(10)*. These two agents facilitate cyst healing by combining their osteogenic (ABM) and osteo-inductive/conductive (DBM) potentials. From September 2008, the same technique was used for both ABCs and SBCs and a precise volumetric follow-up was performed thanks to MRI. Magnetic Resonance is indeed known as the modality of choice considering those lesions *(11)*.

This present article evaluates the effectiveness of ABM associated with DBM during a minimal follow-up of 2 years in 27 patients with either ABC or SBC. Follow-up coupled imaging with clinical evaluation: the ability to perform activities without pain, restrictions or refractures was assessed.

MATERIALS AND METHODS

We obtained the agreement of the local ethics committee of the hospital with the following number: B403201523492.

From September 2008 to August 2018, 27 patients were operated on and included in this cohort study. The last follow-up stopped in January 2021. There were 6 ABCs and 21 SBCs.

We used MRI evaluation for 25 of the 27 patients, allowing the measure of the cystic volume by fluid segmentation *(12)*. The two other patients had MRI contraindication.

The diagnosis of ABC and SBC was based on imaging and verified with histological analyses of biopsies. None of the ABCs were secondary to malignant tumors.

In addition to the age of the patients and the locations of the cysts, other data were collected prior to procedure: tenderness or pain, previous fracture, previous interventions, the distance from the physis. The fracture risk was evaluated as well.

Over the same time period, 18 patients with bone cysts referred to the lead author were excluded. Six cysts (1 ABC and 5 SBCs) did not fulfill the minimum 2 years of follow-up. Nine other SBCs were considered latent and treated conservatively. Three SBCs necessitated simultaneous osteosynthesis along with the first injection (by elastic stable intramedullary nailing) and were therefore excluded as well.

The demineralized bone matrix (DBM) was procured from the registered tissue bank of the hospital. This powder consists of small particles of cortical bone (200 to 800 μm) that were defatted and dehydrated in various solvents as reported previously. Demineralization was obtained with the use of a 0.6-M hydrochloric acid solution (15 mL/g bone) for fifteen hours at 4°C. The particles were rinsed with distilled water until a pH of 5.8 was reached. The powder was then freeze-dried and finally was sterilized with gamma irradiation at a dose of 25 KGy. The final moisture content was <5% of the wet weight. The final product, containing either 2 or 5g of bone particles, was preserved dried in a glass bottle.

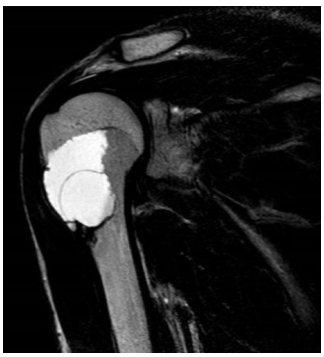

Fig. 1a. — T2-weighted MRI of a 7-year-old boy with a proximal humeral paucilocular aneurysmal bone cyst. He underwent an injection of ABM and DBM.

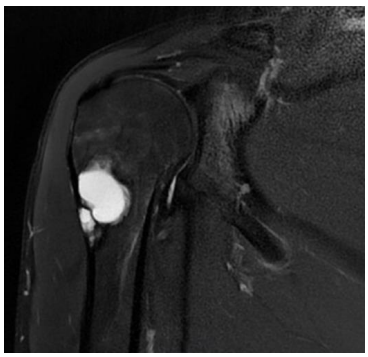

Fig. 1b. — T2-weighted MRI made 2 years after the single injection of treatment. The initial volume shrank to almost a quarter according to volumetric calculation obtained by segmentation. The corticals lost their blown-out character.

Fig. 2a. —T2-weighted MRI of a 9-year-old boy with a proximal humeral multilocular simple bone cyst.

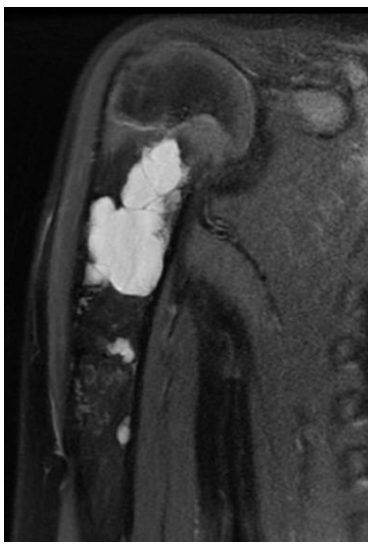

Fig. 2b. — T2-weighted MRI made 1year after the first injection. The cyst decreased in size by two thirds and the cortical thickness was back to normal. However, the cyst diameter was still more than 85% of the bone diameter. Because of this remaining fracture risk, a second injection was performed.

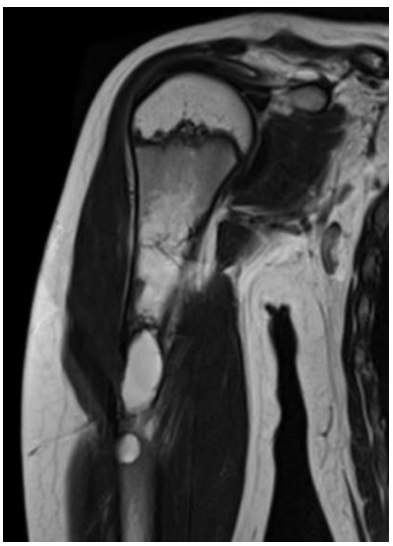

Fig. 2c. —T2-weighted MRI made 6 months after the second injection of treatment. The medulla is now filled by a bone and fat content.

The surgical procedure was performed by a single surgeon with the patient supine under general anesthesia. The cyst was localized with the use of radioscopy. Bone marrow was first aspirated from the anterior superior iliac crest by using a bone marrow biopsy needle (12-gauge diameter; Unimed, Switzerland).

For SBCs, two similar trocars were introduced into both the upper and the lower part of the cavity. The cyst fluid was spontaneously evacuated and

then slowly aspirated. A sample of aspirated cyst fluid was analyzed for cytology. For ABCs, a minimally invasive approach was performed to obtain a small sample of tissue for biopsy. In cases where extemporaneous pathologic analysis of the biopsy did not show malignant cells, procedure was pursued.

The DBM was mixed in equal parts with autologous aspirated bone marrow and was inserted in one or more 10-ml syringe, depending on the cyst volume. The syringe piston was reintroduced for injection. The mixture was injected by the trocars for SBCs or by the mini-approach for ABCs. In case of ABC recurrence with already confirmed diagnosis, a percutaneous technique was used in the same way as SBC. All procedures were performed as one-day surgery.

For the last included patient, corticosteroids were added to the combination of bone marrow and DBM.

For 25 out of the 27 patients, follow-up was performed with MRI every 6 months for 2 years. In case of cyst healing, follow-up was stopped after at least 2 years. Mean follow up lasted 55 months (range 24 to 121 months).

The open-source software ITK-Snap 3.8.0 (www.itksnap.org/) was used to manually segment the cyst on each MRI slice. We calculated the volume of the cyst in the pre- and in the serial postoperative MRIs for each patient. Two different observers performed all the measurements, one of the two being blind of the final result.

In most cases of cyst healing, persistent fluid cavities remained. We considered the cyst healed when the final residual ratio of bone occupied by the cyst (cyst volume/occupied bone volume) shrank to less than 50% of the initial volume ratio. This proportion had to remain stable over time or to continue decreasing 2 years after injection. When healing occurs, cyst fluid is replaced by bone or a mixture of bone and fat. The corticals sag and get thicker (Figs. 1a to 2c).

In some latent healed cases we observe that over years the surrounding bone is growing faster than the cyst is decreasing, allowing for a favorable ratio.

Patients with healed cysts did not experience any new pain and resumed normal activities.

In case of cyst recurrence, the bone graft material was progressively reabsorbed, no sign of consolidation appeared, and the cyst continued to expand.

Two patients (cases 1 and 20) were followed with plain radiographs due to MRI contraindication. The progressive consolidation or recurrence was followed for more than 3 years.

Plain radiographs were used as well to pursue the follow up of the 3 patients who required stabilization with elastic intramedullary nailing (ESIN).

All statistical analyses were performed using IBM SPSS statistics version 27. The p-value of significance was set at $p<0.05$ throughout the study. To compare the results between ABCs and SBCs, a Chi-square test was performed. The 13 previously reported ABCs treated using the same technique were combined with our 6 new patients to allow comparison of the result of the same technique in ABCs (19 patients) and SBCs (21 patients).

In 2005 the lead author published a case series testing the same treatment on 13 ABCs that were active or aggressive cysts *(10)*.

Healing criteria were both radiographic and clinical. The cysts considered as healed were either completely obliterated or adopted a minor remnant form. Both types of healing remained stable with a follow up of at least two years. Patients with healed cysts did not experience recurrence of pain.

MRI were also performed but not on a regular basis: MRI was mainly used in remnant cysts to verify the amount of remaining liquid.

RESULTS

Patients and cyst characteristics are summarized in Table I for ABCs and Table II for SBCs.

All 6 ABCs were considered aggressive according to Campanacci classification *(13)* since they all showed periosteal Codman triangles and soft tissue extension. All patients with ABCs presented with pain.

All 21 SBCs were classified as active and there was a fracture risk based on the common radiographic criteria cited in literature: contact with the physis, cortical thinning, multiple pathologic fractures with no subsequent healing of the cyst.

Table I. — Aneurysmal bone cysts: characteristics and results

ABC Case	Cyst location	Cyst form	Age (yrs.)	Prior fracture	Prior treatment	Number of injections	Cyst status	Imaging appearance	Daily life/ Activities	New fracture	Additional procedures
1	Vertebra	Paucilocular	9	None	/	1	Healed	Disappeared	Normal	/	/
2	Rib	Multilocular	11	None	/	1	Healed	Multilocular	Normal	/	/
3	Malleolus	Unilocular	15	None	/	1	Healed	Disappeared	Normal	/	/
4	Humerus	Paucilocular	19	1	/	1	Healed	Multilocular	Normal	/	/
5	Vertebra	Multilocular	13	None	/	2	Not healed	Multilocular	Normal after curettage	/	Curettage
6	Iliac wing	Paucilocular	15	None	1curettage & bone grafting	1	Not healed	Multilocular	Lost to follow-up	/	Treated in another institution

Table II. — Simple bone cysts: characteristics and results.

SBC Case	Cyst location	Cyst form	Age (yr)	Prior fracture	Prior treatment	Nbr of injections	Cyst status	Imaging appearance	Daily life Activities	Additional procedures	New fracture
1	Femur	Multilocular	9	1	1 bone marrow injection	1	Healed	Multilocular	Normal	/	/
2	Humerus	Paucilocular	13	1		1	Healed	Multilocular	Normal	/	/
3	Iliopubic ramus	Paucilocular	17	None		1	Healed	Multilocular	Normal	/	/
4	Femur	Paucilocular	6	1		2	Healed	Paucilocular	Normal	Epiphysiodesis	/
5	Humerus	Paucilocular	8	1	1curettage & bone grafting	2	Healed	Paucilocular	Normal	/	/
6	Humerus	Unilocular	9	1		2	Healed	disappeared	Normal	/	/
7	Humerus	Unilocular	10	1	1 bone marrow injection	2	Healed	disappeared	Normal	/	/
8	Humerus	Paucilocular	10	1		2	Healed	Multilocular	Normal	/	/
9	Humerus	Unilocular	11	2		2	Healed	Multilocular	Normal	/	/
10	Femur	Paucilocular	18	None		2	Healed	Multilocular	Normal	/	/
11	Humerus	Unilocular	7	None		3	Not healed	Paucilocular	Normal	/	/
12	Humerus	Unilocular	8	1		3	Healed	Paucilocular	Normal	/	/
13	Humerus	Paucilocular	12	1		2	Healed	Paucilocular	Normal	/	/
14	Humerus	Paucilocular	13	None		1	Healed	Paucilocular	Normal	/	/
15	Humerus	Paucilocular	1	1		5	Not healed	Paucilocular	Activities with brace	ESIN*	2
16	Humerus	Paucilocular	2	1		5	Not healed	Multilocular	Normal	/	/
17	Femur	Paucilocular	4	1		3	Not healed	Monolocular	Normal	ESIN	/
18	Humerus	Paucilocular	5	4		3	Healed	Multilocular	Normal	/	/
19	Humerus	Unilocular	7	1		3	Not healed	Monolocular	Restricted activities	ESIN	1
20	Humerus	Unilocular	10	2		2	Healed	Multilocular	Normal	/	1
21	Humerus	Unilocular	12	4		1	Healed	Paucilocular	Normal	/	/

Tenderness to palpation or mechanical pain was found only in six of them.

For ABCs, the location was vertebra in 2 cases, 1 rib, 1 lateral malleolus, 1 humerus and 1 iliac ala. The mean age at presentation was 14 years. None of the ABCs had provoked a pathological fracture and only one ABC had been previously treated by curettage and bone grafting.

For SBCs, the location was the proximal humerus for 16 patients (76%), followed by proximal femur for 4 patients (19%) and there was 1 ilio-pubic ramus location. The mean age at presentation was 9 years. 17 SBC out of 21 (81%) had sustained one pathological fracture. Three patients had undergone one surgery beforehand: 2 injections of bone marrow alone and 1 curettage with bone grafting.

Cyst septation was described in 3 forms: unilocular, paucilocular and multilocular. Paucilocular cysts contain 2 to 10 lacunae. Multilocular cysts count more than 10 lacunae.

Most of the cysts presented with the paucilocular form: 50% of the ABCs and 57% of the SBCs.

The majority of SBCs (81%) presented one or more fractures prior to our treatment. Three patients (14%) refractured after the treatment.

Three patients with SBCs ended with a limb-length discrepancy exceeding 2cm: patient number 18 in his upper limb and patients 4 and 17 in their lower limbs. Only one had undergone epiphysiodesis by the time of redaction of this article.

Results of procedure

No complication occurred due to surgery in any of the 27 patients.

ABCs. Four ABCs healed (67%) with only one single injection. Two evolved to complete disappearance of the cyst and 2 others involuted in minor remnant cysts taking a fine soap bubble appearance.

There were 2 recurrences. One vertebral ABC recurred despite 2 injections and required curettage. This ABC finally healed without complication. The last case recurred after 1 injection. This patient was eventually treated in another institution.

SBCs. Sixteen SBCs healed (76%): 5 after 1 single injection, 9 others after 2 injections and 2 others after 3 injections. There were 2 complete disappearances of cysts and 14 minor remnant cysts (multilocular in 8 cases and paucilocular (less than ten small cavities) in 6 cases).

Five SBCs were considered non-healed. Three of them became latent with no new fractures and with the patient resuming normal activities. Those 5 cysts were considered non-healed as their last MRI calculations showed that they still occupied more than 50% of their initial volume ratio.

Comparison of previous and current cohort of ABCs.

There was no significant difference between the healing rates of the previous series (11 healed ABCs out of 13) and the current one (4 out of 6) (p=0.37).

Comparison of ABCs and SBCs.

There was no significant difference between the healing rates of the ABCs (15 healed ABCs out of 19) and the SBCs (16 out of 21) (p=0.83).

DISCUSSION

This minimally invasive technique offers several advantages for the patient and the surgeon compared to curettage or extensive surgery. It decreases the risk of infection, is easier to perform in poorly accessible locations such as the pelvis or spine and can be safely used in cysts close to the physis.

Another asset is the hemostatic effect of the injected paste. Intraoperative bleeding is common in ABCs and can be stopped by injecting the paste into the lesion. Therefore, no preoperative embolization is required.

In this current series the injection of DBM mixed with autologous bone marrow was effective for both ABCs and SBCs.

After one single injection, healing was achieved in 4 ABCs (out of 6) (67%) and 5 SBCs (out of 21) (24%). After 2 and 3 injections, 9 SBCs (43%) and 2 SBCs (10%) healed. The cumulative rate of SBCs healing after 1 to 3 injections was 76%.

For ABCs, the present rate of healing of 67% was not significantly different from our previous rate of 85% (11/13) (p=0.78).

Despite the better global healing rate for ABCs (79%) compared to SBCs (76%), this difference is not significant (p=0.83).

The limitations of our study include a relatively small number of patients, especially for ABCs.

Current literature about minimally invasive techniques shows variable rates of success even comparing a same treatment. Various healing criteria are used but they lack consensus and are just based on observation of plain radiographs. As the definition of healing differs between articles and knowing the tendency of the cysts to recur, only articles with a minimum of 2 years of follow-up were chosen in order to compare their outcomes.

A few articles tested the treatment (DBM + autologous bone marrow) on SBCs but only one did on ABCs *(10)* and was performed in our hospital. Out of 13 patients: 7 (54%) healed after 1 injection and 4 others (31%) after 2 injections.

Rougraff and Kling *(14)* used the same technique to treat 23 patients with SBCs. They reached higher healing rates with 78% of simple bone cysts healed after one injection and a cumulative 100% success after the second injection. The diagnosis of healing was based on plain radiographs. The cysts that showed graft incorporation and cortical hypertrophy with no recurrence for 2 years were considered healed. The proportion of minor cystic remnants among the healed cysts reached 38% (7 out of 18). None of the treated patients was younger than 4 years old at the time of procedure.

Review articles about current treatments of ABCs mention mainly two new minimally invasive techniques: Polidocanol injections and Denosumab treatment *(15,16)*.

Polidocanol appears to be a safe sclerosant that replaced Ethibloc. Puri and al. *(17)* treated 56 ABCs with intralesional injection of Polidocanol. Healing criteria assessed on plain radiographs were development of sclerosis within the lesion and absence of increase in size. Their results are: 44 % of ABCs healed after a single injection and a cumulative 78% of success after two injections. 16% did not respond to multiple injections and required additional surgery.

Dürr et al. *(18)* used the osteoclasts inhibitor Denosumab on six patients with ABCs. This monoclonal antibody was subcutaneously administered four times in the first month and every month for at least one year. Half of the cysts recurred either during the treatment or up to 24 months after its completion. One patient developed a severe rebound hypercalcemia that required intensive care treatment.

As well as DBM and/or bone marrow, review articles about current minimally invasive treatments of SBCs mainly discuss the intralesional injection of Corticoids or of Calcium Phosphate composite *(19)*.

Methylprednisolone acetate was first tested by Scaglietti in 1974 *(20)* with 90% of "favorable results" and is still widely used. D'Amato et al. *(21)* published in 2019 a therapeutic study comparing the association of bone marrow concentrate with equine-derived demineralized bone matrix (BMC + EDDBM) in 29 SBCs versus Methylprednisolone in 24 SBCs. Healing was achieved when a cyst became partially visible through the surrounded sclerosis or when the cyst was completely obliterated. They concluded that a single injection of BMC + EDDBM provides better results than 3 corticoids injections (83% vs 59%).

Turati and al. performed intralesional injections of a Calcium Phosphate Composite in 13 patients with SBCs *(22)*. No cyst showed recurrence. Ten cysts (76%) were considered healed as Neer A type (no more visible cyst or reduced but still occupies 50% of the medulla diameter) and 3 cysts were classified Neer B type (Modified Neer Outcome Rating System).

In our study we noted different parameters impacting the responsiveness of the cysts.

The high number of fractures prior to surgery is a risk factor of recurrence. Indeed, for the same localization (the humerus), the fact that there was no or 1 fracture before treatment was not linked to recurrence whereas the occurrence of 2 or more fractures prior to surgery was effectively correlated. We can imagine that multiple fractures reflect a high cyst activity that will affect the response to treatment.

Another parameter was the age at the beginning of the symptoms: the only 3 patients younger than 5 years (1, 2 and 4 years old respectively) required 3

to 4 injections and a follow-up of more than 6 years. This is in accordance with observations of several authors that in children younger than 5 years the recurrence rates after intralesional procedures may rise up to 75% *(23)*.

The localization of the cyst showed an influence as well. We cannot demonstrate that this technique is effective in the spine. Two vertebral ABCs starting with the same volume were treated according to our protocol. One recurred considerably after two injections requiring resection whereas, conversely, the second disappeared completely after a single injection.

The number of septa dividing the cyst at presentation was not correlated to success. This could be appreciated with the starting cyst forms (Table I and II). The parameter was checked to verify a correlation between the number of septa cells supposed to respond to the osteo-inductive effect of DBM.

The complications that occurred in our patients are of similar or lower rates compared to those observed with other minimally invasive techniques. There were no specific side effects due to the treatment technique.

Refractures have only been observed in SBCs. The rate was 14% (3 SBCs out of 21). Literature reports 23% to 29% of refractures after other intralesional injections *(24)*.

Limb length discrepancy occurred in 3 SBCs (14%). Stanton et al. *(25)* observed 10% of growth arrest in a study of 51 consecutive patients with SBC of the humerus. Among the 5 affected cysts, 4 had been aspirated and injected with corticoids and one curetted. Other risk factors are discussed in literature with rates of growth arrest in SBCs ranging from 6 to 20% *(26)*.

In summary, the injection of ABM and DBM is a short, easy and safe procedure that offers interesting results compared with current minimally invasive techniques for treating ABCs and SBCs. Caution must be taken comparing outcome results in literature as healing is more easily achieved based on radiographic criteria than on MRI criteria. A consensus based on volume calculation would allow for objective comparison.

A larger patient sample could verify the effectiveness of DBM and ABM in vertebral ABCs.

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