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INSTRUCTIONAL LECTURE: ONCOLOGY

Modern treatment of unicameral and aneurysmatic bone cysts

Elisa Pala, Giulia Trovarelli, Andrea Angelini, Maria Chiara Cerchiaro and Pietro Ruggieri

Department of Orthopedics and Orthopedic Oncology, University of Padova, Padova, Italy

Correspondence should be addressed to P Ruggieri Email pietro.ruggieri@unipd.it

- The best treatment of unicameral bone cyst and aneurismatic bone cyst (ABC) is debated in the literature.
- For simple bone cysts, multiple treatments were proposed from observation only to open curettage. The historical treatment with intraosseous injection of methylprednisolone acetate into the bone cysts nowadays is reduced due to the morbidity of multiple injections and the risk of multiple pathologic fractures until the healing.
- Different types of treatments for ABC are reported, including surgery, percutaneous treatments, and medical treatments; however, there is currently no consensus on the best approach. The association of curettage, bone graft, and elastic stable intramedullary nail (ESIN) had a success rate of over 85%. Decompressing the cyst wall is more critical for increasing the healing rate than the type of graft used to fill the cavity.
- In ABC, sclerotherapy offers the advantages of lower invasiveness and morbidity, associated with better functional scores and faster return to full weight-bearing. Moreover, they can be used in challenging locations.
- Selective arterial embolization is a complex procedure and often requires association with other treatments. Further studies are needed to confirm the effectiveness of denosumab and its side effects on skeletally immature patients. Curettage with adjuvants and autogenous bone grafting still shows promising results and can be used in larger, aggressive defects or superficial lesions.
- For simple bone cysts, the combination of curettage, bone graft, and ESIN showed the best results. Sclerotherapy for ABC also shows promising results.

Keywords: Unicameral bone cyst; aneurismatic bone cyst

Unicameral bone cyst

Unicameral bone cysts (UBCs) are benign, fluid-filled lesions most frequently located in the metaphysis of long bones, especially the proximal humerus and proximal femur (1). In most cases, these lesions are asymptomatic until a pathologic fracture occurs.

The treatment aims to prevent the pathologic fractures, restore the cortical thickness, and contain the recurrence. Multiple treatments have been proposed ranging from observation only to open curettage, and no consensus has been reached on the optimal surgical technique and timing of surgery (2, 3).

Usually, cyst size, presence of symptoms, and risk of pathologic fracture influence the type of treatment.

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Moreover, younger patients have a higher incidence of recurrence; therefore, a more aggressive treatment approach may be chosen (4).

Extended follow-up studies denied the historical belief that most UBCs will resolve with skeletal maturity (5).

In 1979, Scaglietti *et al.* (6) introduced the intraosseous injection of methylprednisolone acetate into bone cysts and suggested repeating the treatment until the cyst healed. However, this treatment is nowadays reduced due to the morbidity associated with multiple injections and the risk of multiple pathologic fractures until the healing occurs (2, 3) (Fig. 1).

A meta-analysis performed by da Ruiz-Arellanos *et al.* (3) showed a healing rate of 44.7% obtained without intervention and only radiological follow-up, compared to up to 70% when injection with corticosteroids, with or without bone matrix, was performed (3).

The high intraosseous pressure caused by venous obstruction and enzymatic lysis is considered responsible for UBC pathogenesis; therefore, the main factor to consider during the surgery is the decompression of the cyst (done with curettage or opening of the medullary canal) (7). When this is not performed, the success rate decreases to 62% (3).

Bone substitute materials seem to be the most effective for filling the cavity, with an efficacy of 87% despite autograft (63%) and allograft (78%) (3).

The association of curettage, bone graft, and elastic stable intramedullary nail (ESIN) appears to be more effective, with a success rate of over 85% (3) (Fig. 2).

Instead, there is no consensus about the right timing for nail removal. Farr *et al.* (2), in an international survey of over 400 pediatric orthopedic surgeons, reported that 2% of respondents remove the implants within 6 months, 35% prefer to wait 6––12 months, and 31% wait more than 12 months after surgery, while 19% never remove the implants (2).

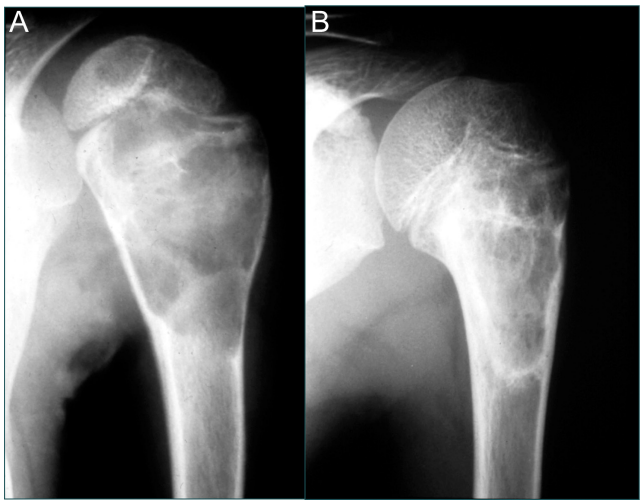

Figure 1

Male, 7 years old. (A) Pathologic fracture on simple bone cyst of the left proximal humerus. (B) Complete healing after three percutaneous corticosteroid injections.

Aneurysmal bone cyst

Aneurysmal bone cysts (ABCs) were first defined in 1942 by Jaffe and Lichtenstein as benign and locally aggressive bone-growing tumor, which accounts for 1% of all bone tumors (1). ABCs occur in children or adolescents with a mean age of 13 years old, and most of the lesions appear before the age of 30 years (8, 9). Common symptoms and signs observed with this lesion are pain, swelling, deformity, and pathological fracture in severe cases (8, 9).

Different types of treatment for ABC are reported, including surgery, percutaneous treatments, and medical treatments; however, there is currently no consensus on the best approach, and the risks and benefits of each treatment must be evaluated according to each individual case.

Criteria for defining healing include pain resolution associated with radiographic signs of ossification, stable disease, or cortex thickening.

Percutaneous treatment

The advantages of percutaneous treatments include lower invasiveness and morbidity, associated with better functional scores and faster return to full weight bearing. Moreover, they can be used in challenging locations (8, 10). On the contrary, the morbidity of multiple procedures with multiple general anesthetics in the pediatric population needs to be evaluated (11) (Fig. 3).

Many sclerosant agents with different application techniques were described: sodium tetradecyl sulfate injected with air to create a foam, or polidocanol, Ethibloc, doxycycline, and calcitonin with steroids injected as liquids (8, 11).

Nowadays, none of these agents has been proven superior to the others, except for Ethibloc and H_2O_2. Nonetheless, these two agents were rapidly abandoned because of the possibility of serious complications like severe acute lung injury (8, 12).

Cruz *et al.* (13), in a meta-analysis including ten studies and 294 patients treated with different sclerosant agents, reported a recurrence-free survival of 94%.

On the other hand, Bavan *et al.* reported a similar failure rate between injection therapies and surgery (11).

Doxycycline can be injected as a foam (combining 200 mg of doxycycline, 5 mL albumin, 25%, and 10 mL of

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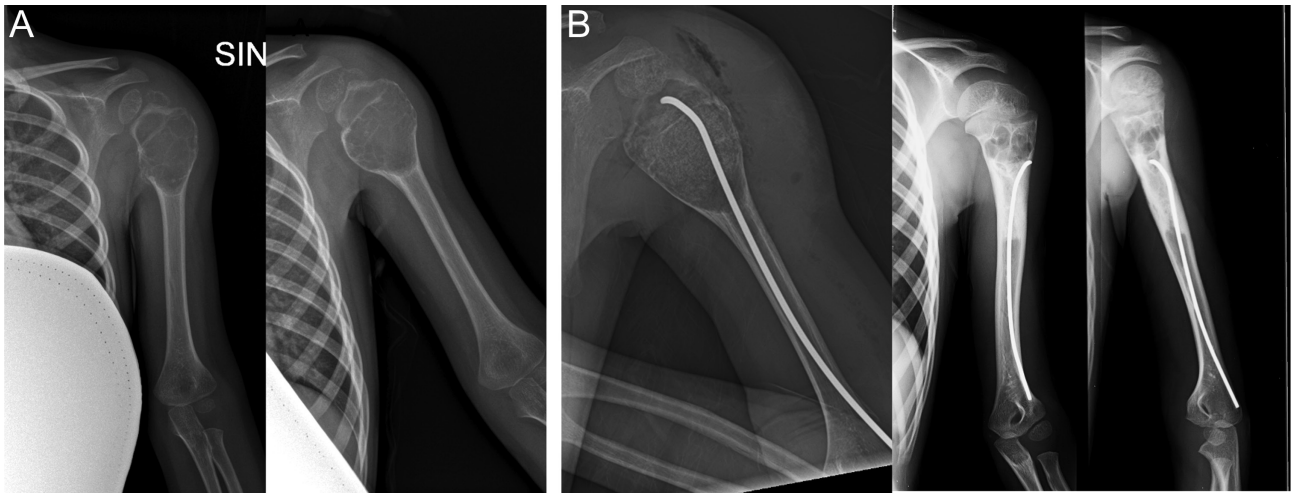

Figure 2

Male, 6 years old. (A) Simple bone cyst of the left proximal humerus. (B) Stabilization with ESIN (only one because of the small canal) and bone grafting with demineralized bone matrix and marrow concentrate. (C) Complete healing after 2.5 years.

air) (14). A rate of complete healing of 94.7% and only a 1.7% recurrence rate were reported after a mean of 3.5 injections of doxycycline/albumin foam. The complication rate was 3.5%, mostly focal skin necrosis (9).

In the case of polidocanol usage, the cyst was injected with 4 mg/kg Polidocanol mixed with a contrast agent every 4–6 weeks until signs of healing were seen (15). Polidocanol sclerotherapy requires a mean of 2.8 injections, ranging between 1.8 and 5.7 (9, 16).

In most of the papers, the healing rate was over 80% (9, 10, 16, 17).

Jasper *et al.* (16) treated 70 patients with polidocanol and reported 83% healing and 75% recurrence-free survival at 5 years.

Weber *et al.* (17) reported 96% complete resolution of pain, 70% complete ossification, and 26% partial ossification without an increase in cyst size after polidocanol injection. They reported no recurrences, and only one case failed to heal and needed curettage and bone grafting.

Complications observed included skin problems (induration, hypopigmentation, minor inflammatory reactions, injection site necrosis, ulceration, or temporary pain), pulmonary embolism, osteomyelitis, allergic responses, and rarely anaphylactic shock (16, 17, 18).

In cases of ABC with pathological fracture, polidocanol may extravasate into soft tissues and cause necrosis. However, in their study, Ahmad *et al.* reported eight

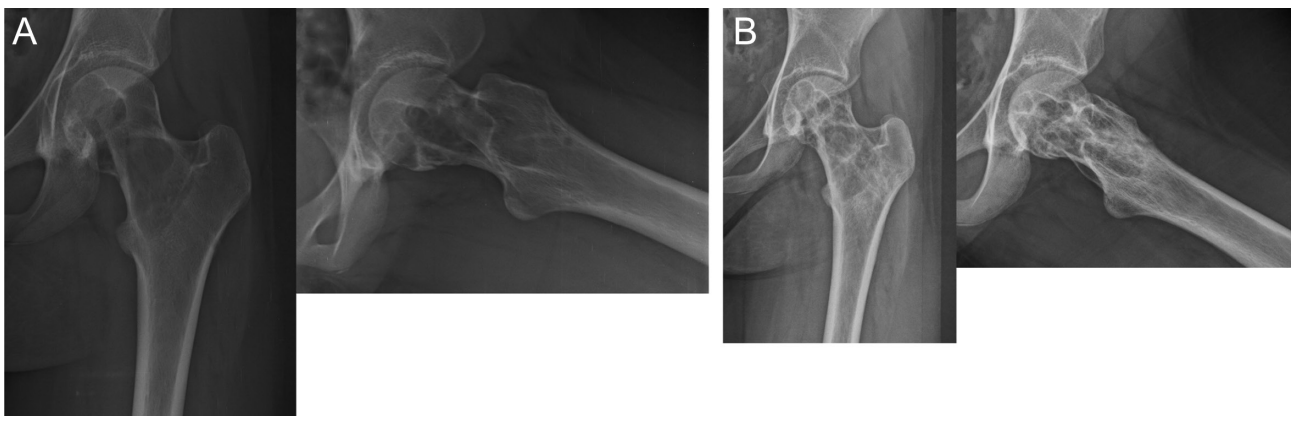

Figure 3

Female, 13 years old. (A) Aneurismatic bone cyst of the left proximal femur. (B) Complete healing after five Polidocanol injection (4 mg/kg every 4 weeks): partial ossification without an increase in cyst size, no uptake of contrast medium on CT, complete resolution of pain.

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cases of ABC with pathological fractures treated with polidocanol sclerotherapy without any complications.

The blood released from the fracture probably created a pseudo-capsule around the cyst, preventing the extravasation of sclerosant (18).

Selective arterial embolization

Embolization is a minimally invasive procedure that blocks the arterial supply to a tumor using variable agents; it is technically demanding because it requires the identification of the vessels that supply the cyst and can potentially create serious side effects due to ischemia (19, 20).

It was initially described for complex cases of ABC, such as the pelvis, spine, and sacrum. Currently, selective arterial embolization is mainly used in association with sclerotherapy or as a neoadjuvant to surgery (13, 21).

In ABC of the pelvis and sacrum, percutaneous procedures with polidocanol, selective arterial embolization, or a combination of the two are successful treatments (21). The local recurrence rate after single or multiple selective arterial embolization was reported to be around 15%, with an incidence of complications around 3%, including skin necrosis, sciatic nerve paresthesia, and artery pseudoaneurysms (9, 13, 22, 23).

Samargandi *et al.* (9), in their meta-analysis, reported 75% complete healing for all sclerotherapy and embolization treatments; they also found a 3.4% recurrence rate. However, they found high heterogeneity and much variation in the results between the studies analyzed.

Surgery

Open surgery with curettage and bone grafting is the standard treatment for ABC (24) (Fig. 4). The incidence of recurrence is 30%, but when high-speed burr and adjuvants are used, this can be reduced to 15% (15, 25).

Local adjuvants such as cement, phenol, alcoholization, argon beam ablation, and cryotherapy have been considered promising adjuvants to minimize local recurrence risk in locally aggressive bone tumors. Among these, the association of curettage, cryotherapy, and bone grafting offers a lower recurrence rate than curettage alone in the case of ABC (24, 26).

Doring *et al.* (4) reported an overall recurrence rate of 31% and a 5-year recurrence-free survival of 66%. They also reported that the recurrence-free survival was lower when phenol was used as adjuvant burring plus autogenous bone graft (4).

Surgery must also be considered in sites with a high risk of skin necrosis, such as hands and feet.

Denosumab

Denosumab is a monoclonal antibody against osteoclast activity that binds to the receptor activator of the nuclear factor kappa-B ligand, inhibiting bone

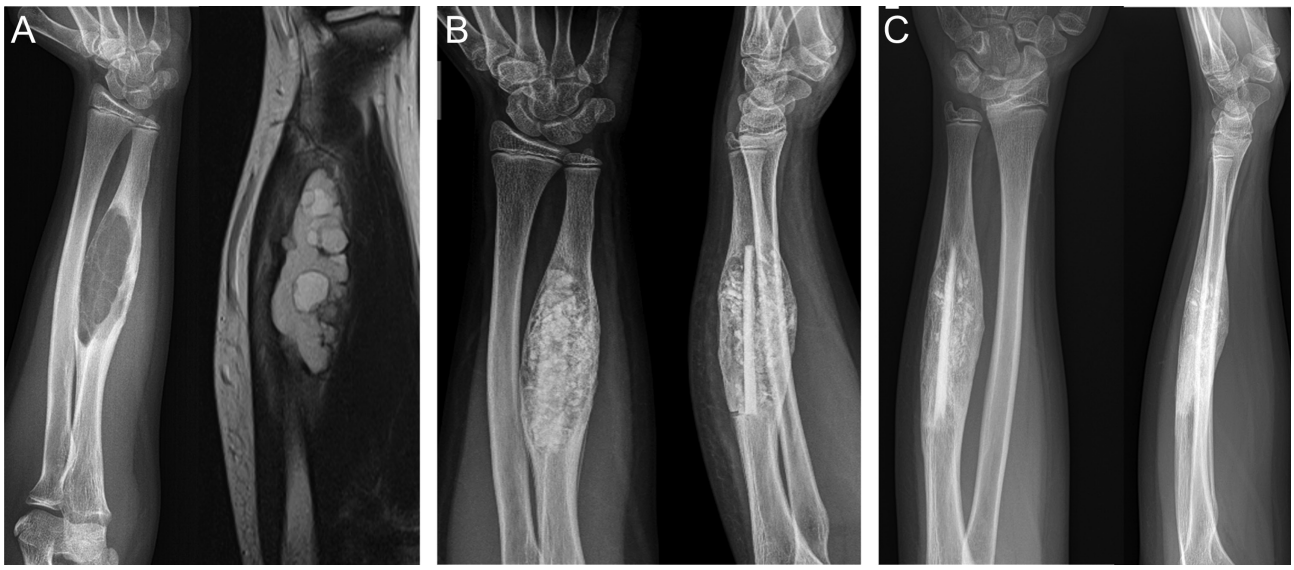

Figure 4

Female, 9 years old. (A) Aneurismatic bone cyst of the ulna. (B) Preoperative embolization, curettage, allograft, and demineralized bone matrix. (C) Complete healing after 6 months.

EFORT Open Reviews (2024) **9** 387–392
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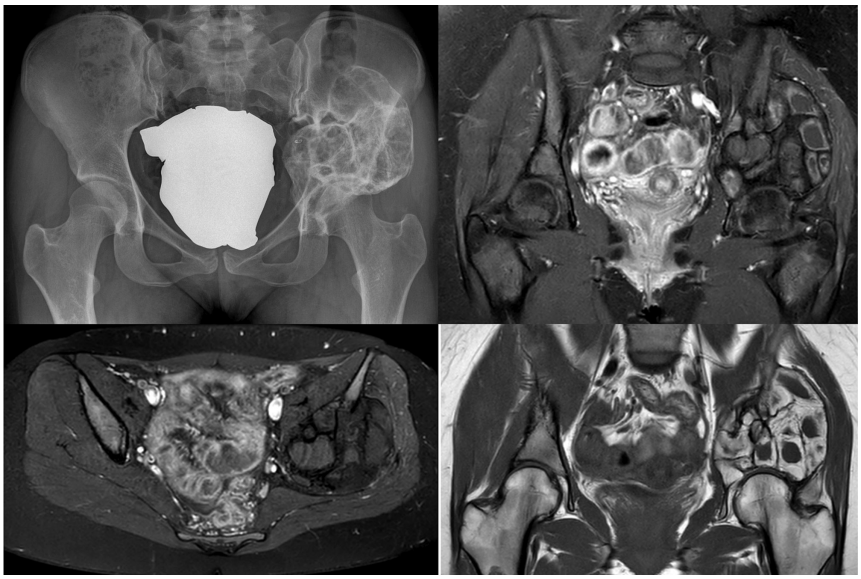

Figure 5

Female, 15 years old. Aneurismatic bone cyst of the left ileum treated with five selective arterial embolization and denosumab for 6 years. Stable disease after 3 years from the last denosumab injection as depicted in the figure.

resorption (27). Several studies reported the efficacy of denosumab in giant cell tumors, reducing tumor mass pre-operatively or in recurrences or inoperable lesions (27). A few papers reported denosumab as an alternative treatment for ABC in cases where surgical resection is not feasible and in recurrent patients where surgery can create potential morbidities (17, 25, 27, 28, 29) (Fig. 5).

However, limited data exist on its use with ABC and its effect in skeletally immature patients (17, 29, 30, 31). Some authors have reported sclerotic metaphyseal bands that appeared during therapy, which migrated away during growth with maintained functionality of the growth plates (31). Moreover, some patients demonstrated severe hypo- or hypercalcemia under or after denosumab treatment (17, 25).

Masry *et al.* reported that a 60 mg dose of denosumab subcutaneously every 6 weeks is sufficient to obtain results without the risk of hypocalcemia for ABC (25). Masry *et al.* (25) reported 80% disease control with only 15% of tolerable drug-related complications.

Conclusion

In simple bone cysts, the most effective treatment appears to be the association of curettage, bone graft, and ESIN. Decompressing the cyst wall is more critical to increase the healing rate than the type of graft used for filling the cavity. Bone substitute seems to be more effective than autograft.

In ABC, the treatment depends on the site and size of the lesion. Sclerotherapy offers good results but requires multiple procedures. Selective arterial embolization is a challenging procedure and often needs association with other treatments. Further studies are needed to confirm the effectiveness of denosumab and its side effects on skeletally immature patients. Curettage with adjuvants and autogenous bone grafting still shows promising results. and can be used in larger, aggressive defects or superficial lesions.

ICMJE Conflict of Interest Statement

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