

Recurrent Pelvic Aneurysmal Bone Cyst Treated With Doxycycline: A Case Report

Dr. T Robert 1, Beddina 2 and Dr. Nimal 3

¹University of South Asia

²College of Medicine

³University of South Asia

Abstract

Background: Aneurysmal bone cysts (ABCs) are locally aggressive, non-cancerous bone lesions that are rare, most commonly occur in children (75% of patients are < 20 yrs 1), and typically continue to spread until treated. They have a high risk of recurrence [1].

Methods: We present an 11-year-old female with a recurrent ABC of the pelvis, involving the right pubic ramus, ischium and medial wall of the acetabulum. She was treated initially with curettage and bone grafting but was discovered to have recurred at two-year follow-up. She was successfully treated with repeat curettage with iliac bone grafting and doxycycline as a sclerosing agent.

Results: At two and three-month follow up visits the patient continues to ambulate well, and radiographs demonstrate healing with successful graft incorporation and no sign of recurrence.

Conclusion: At the time of this publication, there were no reports detailing the use of doxycycline as a sclerosing agent for recurrent pelvic ABCs as extensive as the case presented here. However, doxycycline has been recently reported as efficacious in the treatment of other recurrent ABCs, primarily through percutaneous administration.

Introduction

Bone tumors can be classified according to the matrix or substance they produce [2]:

1. Bone-forming tumors (osteoid osteoma, osteoblastoma)
2. Cartilage forming tumors (osteochondroma, chondroma, chondroblastoma, chondromyxoid fibroma)
3. Fibrous lesions (fibrous dysplasia, ossifying fibroma, non-ossifying fibroma)
4. Cystic and vascular lesions.

ABCs are classified as cystic and may be further classified as primary or secondary according to their etiology and account for approximately 1% of all primary benign bone tumors [3]. Although they can be found in any region, they are most commonly located within the posterior spinal elements, femur, and tibia [4]. It is estimated that 20-70% of treated ABCs recur in the first couple of years after treatment. Until recently, ABCs were thought to result from a malfunctioning venous network within the bone, leading to dilation and rupture of local vasculature, but studies suggest that the underlying pathology may be due to arteriovenous fistulas developing within the bone [5]. The true cause is still uncertain [6]. Excision with curettage and bone grafting is considered the standard of treatment for these lesions [7]. Although various treatment options for recurrent ABCs have been suggested, doxycycline is emerging as a viable treatment option, and its use has been documented for lesions throughout the body [8].

Case Presentation

Our patient is an 11-year-old, African American female referred for functional groin pain for one year. History and physical exam were negative for constitutional symptoms, bowel or bladder symptoms, or vascular issues. She had no lower extremity motor or sensory deficits. Pain with full flexion of the right hip was noted. Plain radiographs of the pelvis (Figure 1) demonstrated an expansile lesion involving the

right superior ramus, medial wall of the acetabulum, and ischium. MRI was obtained to further characterize the lesion, which showed a 7.0 x 5.4 x 5.3 cm expansile, intraosseous, multiloculated lesion with fluid-fluid levels involving the right superior pubic ramus and ischium consistent with an ABC (Figure 2). She subsequently underwent curettage with demineralized bone matrix and cancellous allograft.

Follow up

The patient did well postoperatively with improvement in



Figure 1: Preoperative inlet (A) and (B) radiographs of the pelvis demonstrating a cystic bony lesion of the right anterior hemipelvis.

***Corresponding author:** Dr. Robert MD, University of South Asia, E-mail: robert@usae.edu

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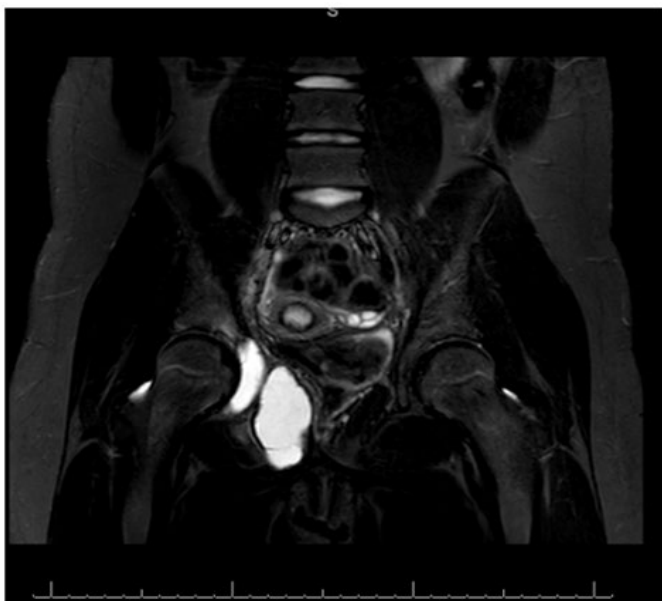


Figure 2: Coronal MRI of the pelvis showing cystic lesion with fluid levels consistent with ABC.



Figure 3: AP radiographs of the pelvis at two months (A) and four months (B) following the index procedure demonstrating no significant change or recurrence.

symptoms. She could ambulate without pain and had full range of motion of the lower extremities bilaterally. No neurologic abnormalities were noted. Imaging of the pelvis revealed no change in the size of the mass over a six-month period (Figure 3). The patient was lost to follow up and returned 2 years later with complaints of recurrent right-sided hip pain for one year, exacerbated by daily activities such as walking and jumping. Physical exam demonstrated tenderness to palpation over the right superior ramus and pain with hip flexion. Imaging revealed the cystic area had increased in size compared to imaging studies two years prior with increasing lucency and multiple septa noted (Figure 4). The patient underwent repeat curettage with posterior iliac crest bone grafting augmented with cancellous allograft and doxycycline administration as a sclerosing agent.

Surgical Technique

A posterior iliac crest bone graft was first obtained with the patient in the prone position. She was then placed supine. Fluoroscopic visualization was used to determine the correct entry point over the involved superior ramus. A roughly 3 cm longitudinal incision was made over the ramus, medial to the femoral neurovascular bundle (Figure 5). The cyst was readily identified, and its thin wall allowed easy entrance with blunt instrumentation (Figure 6). A window, approximately 1x1 cm in dimension, was created using a Kerrison rongeur. The rongeurs were then used to break up the thin, deeper septa and remove membranous tissue. Curettage was performed, removing

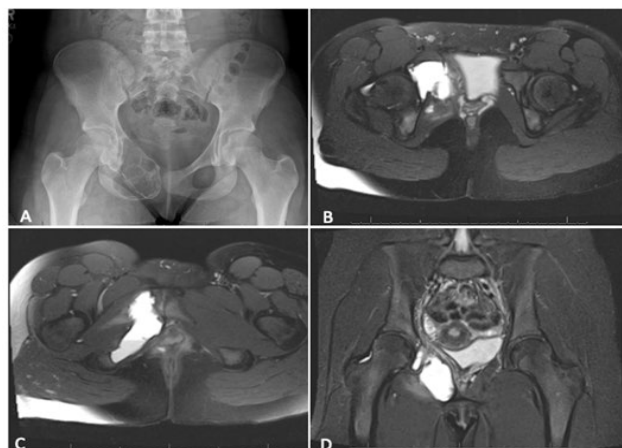


Figure 4: AP Pelvis XR (A) and MRI sequences (B, C, D) showing degree of cyst recurrence with multiple septa and fluid-fluid levels.



Figure 5: Initial incision was made over the superior pubic ramus.

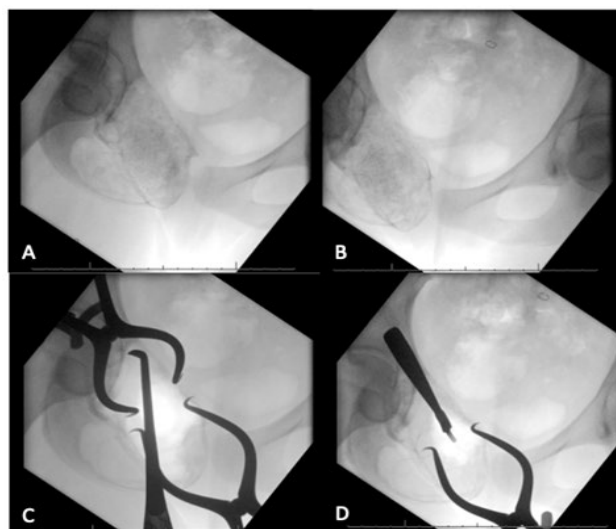


Figure 6: Live fluoroscopy showing cyst dimensions (A, B) and blunt removal of septations and membranous tissue (C, D).

the remaining cyst wall tissue which was sent for pathology. Under fluoroscopic visualization, extensions of the cyst were probed with a curette to ensure all walls were accessible. The cyst was then irrigated with normal saline. 300 mg of doxycycline was diluted in 3 mL of normal saline and delivered along the cavity walls. The cyst was subsequently filled with morselized iliac crest bone graft and demineralized bone matrix (DBM). All parts of the cyst except the deepest portion of the ilium, which was difficult to access, appeared well-grafted.

Outcomes and Follow-up

At her two-week and three-month follow-up visits, the patient was convalescing well and ambulating without difficulty. On exam, the incision at the right pubis was well-healed without obvious infection. The posterior iliac crest incision site was also well-healed. Radiographs at each respective visit showed increasing graft incorporation and homogeneity. (Figure 7, Figure 8). The patient will have regular, 6-month visits to assess her long-term outcome.



Figure 7: AP pelvis radiograph at two weeks post-op showing initial graft incorporation with a small area of residual lucency in the ischium.



Figure 8: AP pelvis radiograph at 3-month post-op showing graft incorporation with improved homogeneity.

Discussion

Aneurysmal bone cysts are slightly more common in females and often associated with USP6 gene rearrangement [9], with a high recurrence rate (~ 25%), particularly in younger children. Until recently, ABCs were considered a non-neoplastic process of unknown etiology, and this was supported by several reports [10]. However, it is now reported that the chromosomal translocation t (16; 17) (q22; p13) is responsible for cytogenetic abnormality in ABCs, suggesting a neoplastic etiology in these lesions [11]. Multinucleated giant cells in ABCs are highly osteolytic due to high levels of matrix metalloproteinases (MMP-9 and MMP-10), tartarate-resistant acid phosphatase, and cathepsin K [12]. Osteolytic lesions of bone consequently increase levels of vascular endothelial growth factor (VEGF) in addition to MMPs [13].

Further, 30% of all ABCs are associated with other tumors, including giant cell tumors, chondroblastoma, fibrous dysplasia, and chondromyxoid fibroma [14]. The judicious use of denosumab or bisphosphonates has been shown to augment the efficacy of surgical management in cases of recurrence [15]. However, these anti-angiogenic drugs are not without their side effects. There is ongoing research to discover less toxic treatment options [16].

The tetracycline antibiotic, doxycycline has been safely used for over 50 years for many conditions including acne, rosacea, and a variety of bacterial and parasitic infections [17]. One of the well-known side effects of doxycycline is that of suppressed bone growth in infants, children, and adolescents, and its routine, systemic use is contraindicated in these populations. This dose-related side effect is due to the calcium-binding effect of doxycycline which affects calcium orthophosphate metabolism. This is shown to occur after just one systemic dose, resulting in restricted bone growth [18]. Doxycycline has been well documented in its use as an anti-cancer agent [19]. It selectively reduces cellular respiration through restriction of mitochondrial protein translation, specifically the expression of four mitochondrial DNA encoded proteins (MT-ND3, MT-CO2, MT-ATP6, and MT-ATP8) by up to 35-fold [20]. This proves useful in targeting cancer cells which, due to their rapid, unregulated growth, require increased cellular respiration to survive [21]. This off-target effect poses doxycycline to be a potentially effective treatment option in the case of ABCs with modest systemic side effects, particularly with local administration rather than systemic dosing.

Doxycycline has demonstrated the healing of lymphatic malformations associated with elevated VEGF and MMPs [23]. In bone and soft tissue tumors, doxycycline demonstrates antitumoral properties thought to be due to the inhibition of MMP and factors involved in angiogenesis²³. Additionally, Doxycycline has demonstrated inhibition of osteoclastic function, and induction of osteoclastic apoptosis [24]. One study demonstrated the effectiveness in percutaneous treatment of ABCs with doxycycline with 43% of patients experiencing resolution of symptoms after a single treatment [25].

Conclusion

Aneurysmal bone cysts (ABCs) are rare, highly destructive benign bone tumors, occurring in 1.4 to 3.2 people per 1,000,000 annually²⁶. The morbidity of an ABC can be substantial depending on the location and size of the lesion. Due to the etiology of ABCs and their close association with other cancers, vascular and neurological conditions, caution should be taken when addressing these lesions and approached with a multidisciplinary team. Current treatment

may be augmented with sclerosing agents such as anti-cancer drugs, which can have harmful side effects. These effects may be mitigated with the use of doxycycline, whose anti-cancer properties and more desirable toxicity profile are proving to be beneficial in this population. Continued follow-up with our patient will hopefully help add to the current literature supporting doxycycline's use in treating recurrent ABCs.

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