

Doxycycline Injection Treatment for Unicameral Bone Cysts: a Case Series

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Abstract

Background: Unicameral bone cysts (UBCs) are frequently associated with pathologic fracture due to aggressive osteolysis.

Methods/Results: We present a case series (n=5) with complex or refractory bone cysts treated with doxycycline injections that exhibited increased ossification and symptom resolution at short term follow up with minimal side effects.

Conclusions: In addition to its antibiotic properties, doxycycline is also known to inhibit matrix metalloproteinases, angiogenesis, and osteoclast activity suggesting that UBCs are dependent on MMP, VEGF or RANKL-mediated osteolysis. Further investigation is warranted regarding the use of doxycycline injections in UBCs.

Background

The unicameral bone cyst (UBC) is a benign bone lesion often occurring in the metaphysis of long bones or within the axial skeleton. The UBC consists of fluid-filled cavities that can enlarge over time thinning the surrounding bone, and, in some cases, cause significant morbidity as a result of pathologic fracture. Of all UBCs, 85% occur in childhood and adolescence, with a peak between 3 and 14 years of age with a mean age of diagnosis of 9 years.(1,2) UBCs are uncommon in adults, demonstrating potential spontaneous resolution and a good prognosis for pediatric patients.(3) They represent 3% of all biopsied bone lesions and are twice as common in males compared to females.(4) Risk factors associated with pathologic fractures in UBC patients include male sex, increased bone width, thinned bone cortex, and location in a long bone.(5)

The selected treatment depends on many factors including the severity of pain, age of patient, location of lesion, and history of pathologic fracture.(6) Treatment for UBCs include observation versus active treatment options such as autologous bone marrow injections, steroid injections, injection of demineralized bone matrix, decompression, and curettage with bone graft. Although there is no clear consensus on the best treatment modality, a meta-analysis found that active treatment over observational treatment had improved healing rates and that no one modality was consistently more effective than another.(7) Our case series identifies a new potential treatment option for UBCs consisting of an intralesional doxycycline injection.

Doxycycline is an antibiotic that also inhibits human matrix metalloproteinases (MMP) and vascular endothelial growth factor (VEGF).(8,9) It demonstrates antitumoral properties in both bone and soft tissue not only by inhibiting matrix degradation and angiogenesis, but also by inhibiting osteoclast function and survival.(9–12) Most recently, doxycycline injections were proposed as a treatment option for aneurysmal bone cysts (ABC), benign, locally aggressive tumors. Like UBCs, ABCs are associated with aggressive osteolysis. Following doxycycline injections, ABC lesions ossify in a predictable fashion resulting in a durable treatment response.(13) To date, doxycycline injections have not been evaluated in the treatment

of UBCs. We now present a case series documenting successful initial treatment of complex or refractory UBCs with intralesional doxycycline injections.

Methods

Ethics statement

All procedures relating to the acquisition of information were approved by the Van Andel Institute and Spectrum Health Institutional Review Boards. Written informed consent was obtained from each subject before participating and was obtained from the patient's guardian for doxycycline treatment. Each subject consented to research participation and publication. This manuscript conforms to principles of the Declaration of Helsinki and has been approved by our institution's institutional review board. The use of doxycycline for UBCs is not currently approved by the FDA and is considered "off-label."

CT-guided intralesional doxycycline injection method

The typical procedure was conducted as described in the following paragraph. Patients typically required two rounds of doxycycline injection separated by ~2 months. Doxycycline (10mg/mL) was used as the chemical ablation agent and delivered as a protein foam, a mixture of doxycycline and 25% albumin agitated with air to create the stable protein foam delivery system.⁽¹³⁾ A total of 150mg and 300mg of doxycycline was injected during the first and second rounds. Using incremental CT guidance, a single 18-gauge Chiba needle was carefully advanced into the lytic medullary portion of the UBC (Figure 1a). A second needle was positioned into multiple areas of the lytic bone lesion and small aliquots of doxycycline mixed with 25% albumin and Isovue contrast material were injected (Figure 1b, c). The inner stylets from the remaining 2 Chiba needles were also removed and escape of Doxycycline foam was evident. Intraprocedural CT images showed good distribution of contrast and doxycycline liquid throughout the bone lesion. Both needles were removed, hemostasis was achieved, and a sterile dressing was applied. Infusion sessions lasted approximately 50 minutes on average.

Results

CT-guided right proximal humeral bone cyst injection in a 3-year-old male

A healthy 3-year-old male with a history of right arm pain and limited range of motion presented after falling out of his bed. Radiographic imaging showed a right proximal humerus lesion with pathologic fracture (Figure 2a). The patient was referred to orthopedic surgery for further treatment. An initial period of 4 weeks was recommended to allow fracture healing. Despite an initial period of observation, the lesion did not resolve with successful fracture healing. To confirm the diagnosis an open biopsy was performed and showed hyalinized acellular cementum consistent with a UBC.

Treatment options were discussed and the family was amenable to a CT-guided doxycycline injection. A biopsy was performed confirming the presence of a benign UBC. Two consecutive doxycycline injections

were then performed within 3 months.

Routine follow-up after the first doxycycline injection showed noticeable improvement in the patient's discomfort and range of motion. The patient was cleared for normal activity due to decreased fracture risk as a result of intralesional ossification and increased cortical thickening. One month after the second injection, the patient was asymptomatic and had resumed normal activity with near normal range of motion. Repeat radiography at that time showed complete resolution of the UBC lesion with dense ossification and remodeling of the proximal humerus expansion (Figure 2b). The patient required occasional Tylenol following each procedure and no other complaints or complications were noted.

CT-guided left proximal humeral bone cyst injection in a 9-year-old male

A healthy 9-year-old male presented to the emergency room with atraumatic left shoulder pain. Radiographs demonstrated a lytic lesion of the left proximal humerus with visible septations and mild expansion of the cortical bone suggesting a UBC with a pathologic fracture (Figure 3).

Orthopedic review was not conclusive for UBC as a focal area of multiple septations was present on MRI suggesting the possibility of a secondary ABC, therefore an open biopsy was performed in the area of concern to establish a definitive diagnosis. The biopsy demonstrated fragments of membranous stroma with spindle cells, occasional giant cells, and focal recent hemorrhage and hemosiderin. Samples taken were negative for rearrangement of the USP6 (17p13.2) gene region, a gene strongly associated with ABC pathology thereby confirming the diagnosis of UBC.

Given these findings, the family elected to undergo CT-guided intralesional doxycycline injections after an initial period of 4 weeks of observation and weight bearing restriction to allow fracture healing, during which time the lesion did not resolve. An interventional radiology specialist conducted two rounds of doxycycline injections performed two months apart with the technique previously described. Serial radiographs demonstrated progressive resolution of the UBC with rapid ossification of the lesion, as well as decreasing expansion of the left proximal humerus (Figure 3b, c). The patient required occasional Tylenol following each procedure. No other complaints or complications were noted.

CT-guided left proximal humeral bone cyst injection in a 10-year-old male

A healthy 10-year-old male presented to the emergency department with a radiographically-diagnosed pathologic fracture of his left proximal humerus after playing flag football (Figure 4a). He was initially treated in a sling for 4 weeks and regained full ROM and strength upon successful fracture healing. Approximately 3 months after the original injury, the patient reported intermittent pain, and radiographs showed persistence of the UBC (Figure 4b). After discussion of treatment options, the parents elected for CT-guided intralesional doxycycline injections. The patient received 2 injections approximately 10 weeks apart. At a follow-up visit of 2 months after the second injection, the patient had normal use of his arm without pain and radiographs demonstrated increased consolidation of the UBC with increased cortical thickness. (Figure 4c). It was determined in the second procedure that there were minimal cystic portions

of the lesion to inject in the future so he is currently being observed for recurrence. The injections were well-tolerated without complications apart from mild discomfort requiring Tylenol immediately post-procedure.

CT-guided right pelvis bone cyst injection in a 12-year-old female

A healthy 12-year-old female was evaluated in the emergency department for right hip pain after falling off of a trampoline. Initial imaging showed a UBC of the right ischium without evidence of pathological fracture (Figure 5a). The patient was ambulatory with a mild limp and improved with physical therapy until returning to the ED a few months later with the same complaint of right hip pain. Radiographs demonstrated size progression in the UBC necessitating treatment (Figure 5b). The patient was then referred to orthopedic surgery and after a discussion of treatment options, underwent serial doxycycline injections.

Three doxycycline injections were performed at 10-week intervals. The procedures were tolerated well with no complications or reported side effects. Remodeling and ossification of the UBC progressed over the course of three doxycycline injections (Figure 5c). The patient was symptom free after the first injection and was released to full activity after the second injection.

CT-guided right distal radius bone cyst injection in a 7-year-old female

A healthy 7-year-old female presented with a history of recurrent pathologic fractures of the right distal radius though a progressive UBC. Radiography revealed a expansile lytic lesion with a fallen fragment sign consistent with a pathologic fracture through a UBC (Figure 6a).

The fracture healed with nonoperative treatment in a splint for 4 weeks, but the bone remained expansile and the UBC failed to resolve. After discussion with the patient and family regarding potential treatment options, the family elected for treatment with CT-guided intralesional doxycycline injections which were performed 10 weeks apart. Radiographs taken after each injection demonstrated incremental cortical remodeling and ossification of the UBC lesion (Figure 6b, c). Follow up radiographs at 2 months and 9 months after the second injection, show increased ossification and cortical thickening (Figure 6c, d). She remained asymptomatic though her most recent follow-up, 10 months after the second injection. The patient and family denied any complications or treatment side effects apart from early mild post-procedural discomfort managed with Tylenol.

Discussion

We present data confirming the successful initial treatment of 5 independent cases of UBCs using doxycycline injections. Although the clinical time frame is limited to the initial treatment period and there is limited long term follow up, this proof-of-principle study provides scientific and clinical rationale for further investigation of this technique. Our indication for doxycycline injections was complex presentations of UBCs such as pathologic fracture or failure of observation. In each case the diagnosis of

UBC was established using radiologic criteria or, if secondary ABC was suspected, biopsy was performed with molecular diagnostic confirmation. Given the rapid ossification and bone remodeling observed in each case, our data provides sound rationale for studying this technique more broadly in primary, uncomplicated presentations of UBCs. In the past, doxycycline has been proposed as a treatment for ABCs, however based on an extensive search of the literature, there are no reports of it being used in UBCs.

Our main surgical indication was prior pathologic fracture or failed period of initial observation. The diagnosis was confirmed radiographically based on x-ray appearance unless there were overlapping features with another benign bone lesion such as an ABC. The use of biopsy for UBCs is not always necessary, however if an ABC is in the differential it is important to perform a thorough workup that includes molecular diagnostics as ABC treatment typically requires a different management approach. Common intralesional injections for UBCs are methylprednisolone, autologous bone marrow and demineralized bone matrix(2) but not doxycycline. To the best of our knowledge, this case series is the first to describe UBC resolution after intralesional doxycycline injection. Progressive ossification of the UBCs was observed as early as 6 weeks after CT-guided intralesional doxycycline injections as seen in figure 3b. We are confident that the observed mineralization was ossification based on the emergence of radiographic findings such as trabeculation, restoration of corticomedullary junctions, and measurable increases in cortical thickness.

From a mechanistic standpoint, doxycycline is known to mitigate protein synthesis in bacteria through inhibition of the ribosomal 30s subunit. *In vitro* data also confirms antitumoral and anti-metastatic effects in multiple types of malignancies including melanoma, breast carcinoma, pancreatic cancer, and ovarian cancer, granted it is not currently used as a cancer treatment agent.(14–17) Doxycycline has also been shown to inhibit cell growth and enzymatic activity in human osteosarcoma through its effect on MMP activity and restoring apoptosis mechanisms.(11) Relevant to UBC pathogenesis, doxycycline has anti-resorptive properties in bone as it suppresses osteoclastogenesis by inhibiting MMP-9-mediated receptor activator of nuclear factor-kappa B ligand (RANKL) expression.(18)

One of the hallmarks of UBC histopathology is abundant osteoclasts in the lining tissue suggesting that RANKL may play a critical role in local osteoclast recruitment and activation similar to what is observed in ABCs.(19,20) Doxycycline is also a calcium chelator thereby interfering with bone remodeling.(21) Therefore, it is likely that doxycycline works through multiple mechanisms to reverse UBC-mediated osteolysis.(9–12) Conceivably, the anti-resorptive effects of doxycycline alone would not explain the robust bone formation observed in each of the 5 cases. There is mixed evidence as to whether doxycycline exhibits any anabolic effects in bone that would explain the robust bone formation we observed during treatment.(22,23) RANKL is strongly coupled to osteoblast differentiation and activation, so there may be a potent activation of osteoblast activity that commonly occurs in the setting of RANKL inhibition.(24) More work is needed to determine how doxycycline simultaneously inhibits bone resorption and stimulates bone formation in the context of UBCs.

Another potential mechanism through which doxycycline injections may be acting is based on the theory that UBC formation is caused or supported by vascular phenomena around the lesions. Venous congestion has been observed, as well as significant venous outflow during contrast injections into cysts. Doxycycline has been shown to block intimal thickening through inhibition of smooth muscle cell proliferation and migration.(25) Thus, another explanation for doxycycline's effectiveness may be due to inhibition of smooth muscle proliferation which, in turn, is modulated by MMP-2 and MMP-9.(25) It has also been postulated that vasoconstriction may result in occlusion of the intramedullary circulation within a UBC thus decreasing intralesional pressure. This may remove a critical factor in UBC persistence and ultimately set the stage for lesion consolidation. In our series, the vasculature surrounding the UBC lesions was routinely assessed with injected contrast and was unremarkable (data not shown).

Serious side effects are rare with doxycycline. It should be noted that tetracycline class antibiotics are associated with tooth discoloration and dental enamel hypoplasia in young (<8yo) pediatric patients with prolonged use. To date, no side effects have been reported following intraosseous injection apart from local soft tissue irritation if spillage occurs.(9) Soft tissue toxicity is a concern with concentrated doxycycline injections as it is commonly used to stimulate fibrosis such as in chemical pleurodesis.(26) Nonetheless, given the lack of observed side effects it appears that doxycycline is potentially a safe, minimally invasive treatment option for symptomatic lesions or lesions presenting with impending or actual pathologic fracture.

Conclusion

This paper demonstrates five examples of the successful short-term treatment of UBCs using CT-guided intralesional doxycycline injections. There were no adverse reactions reported apart from mild post-procedural discomfort. Broader use of doxycycline should be studied in the treatment of UBCs.

Abbreviations

UBC: Unicameral bone cyst

ABC: Aneurysmal bone cyst

Declarations

Ethics approval and consent to participate

All procedures relating to the acquisition of information were approved by the Van Andel Institute and Spectrum Health Institutional Review Boards. Written informed consent was obtained from each subject before participating and was obtained from the patient's guardian for doxycycline treatment. This manuscript conforms to principles of the Declaration of Helsinki and has been approved by our institution's institutional review board. The use of doxycycline for UBCs is not currently approved by the FDA and is considered "off-label."

Consent for publication

Each subject consented to research participation and publication.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

All authors were involved in every step of this case series. All authors read and approved the final manuscript.

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Figures

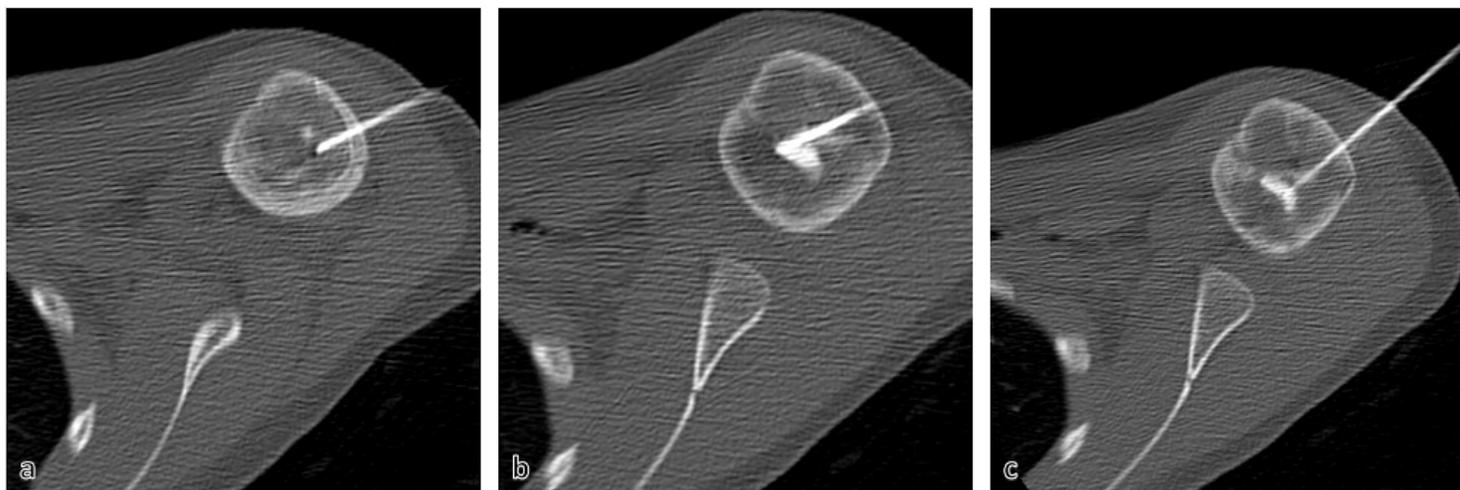


Figure 1

CT-guided doxycycline ablation of a left proximal humerus bone cyst

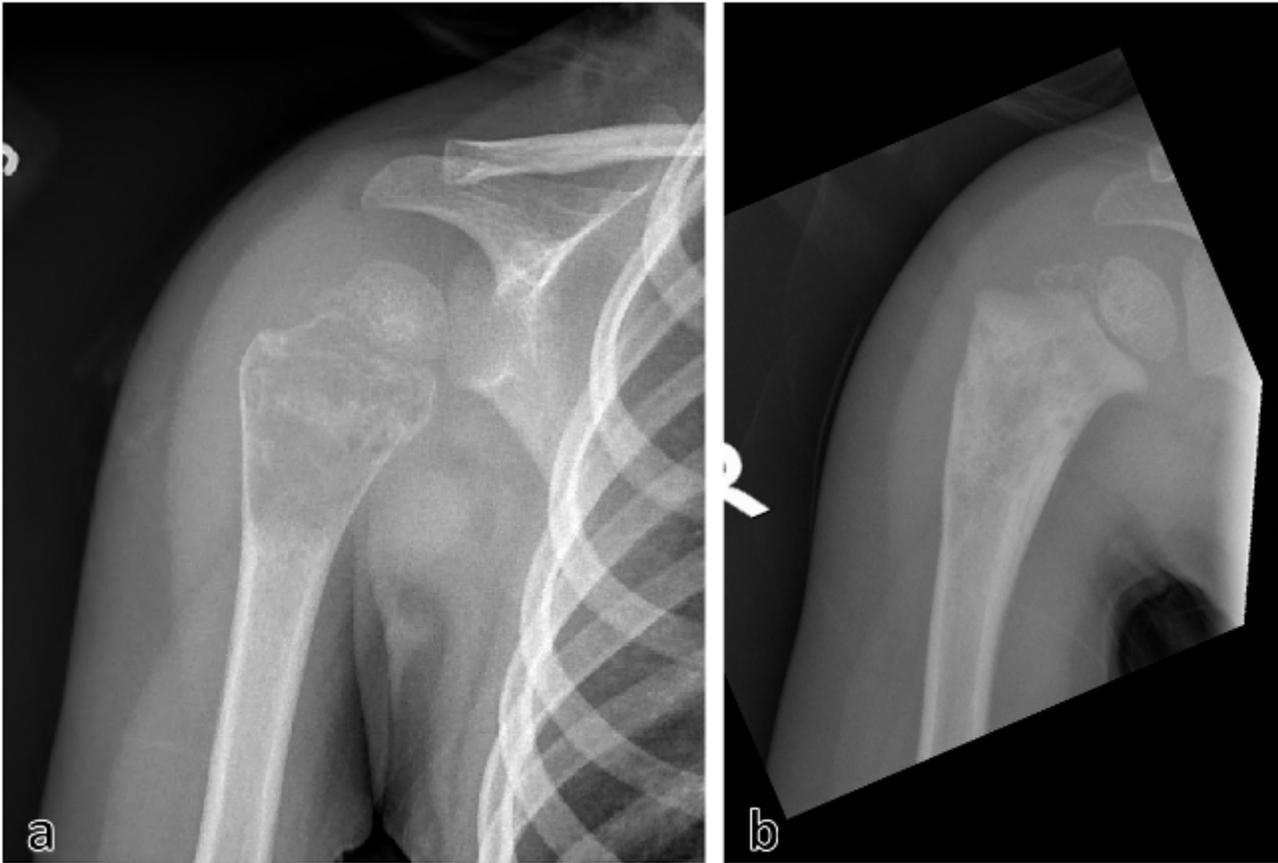


Figure 2

Consecutive right proximal humerus radiographs demonstrating consolidation of a lucent, expansile proximal metadiaphyseal lesion consistent with UBC performed at time points: a. 1 month prior to the first doxycycline injection and b. 1 month after the second doxycycline injection (3 months after doxycycline initiation).

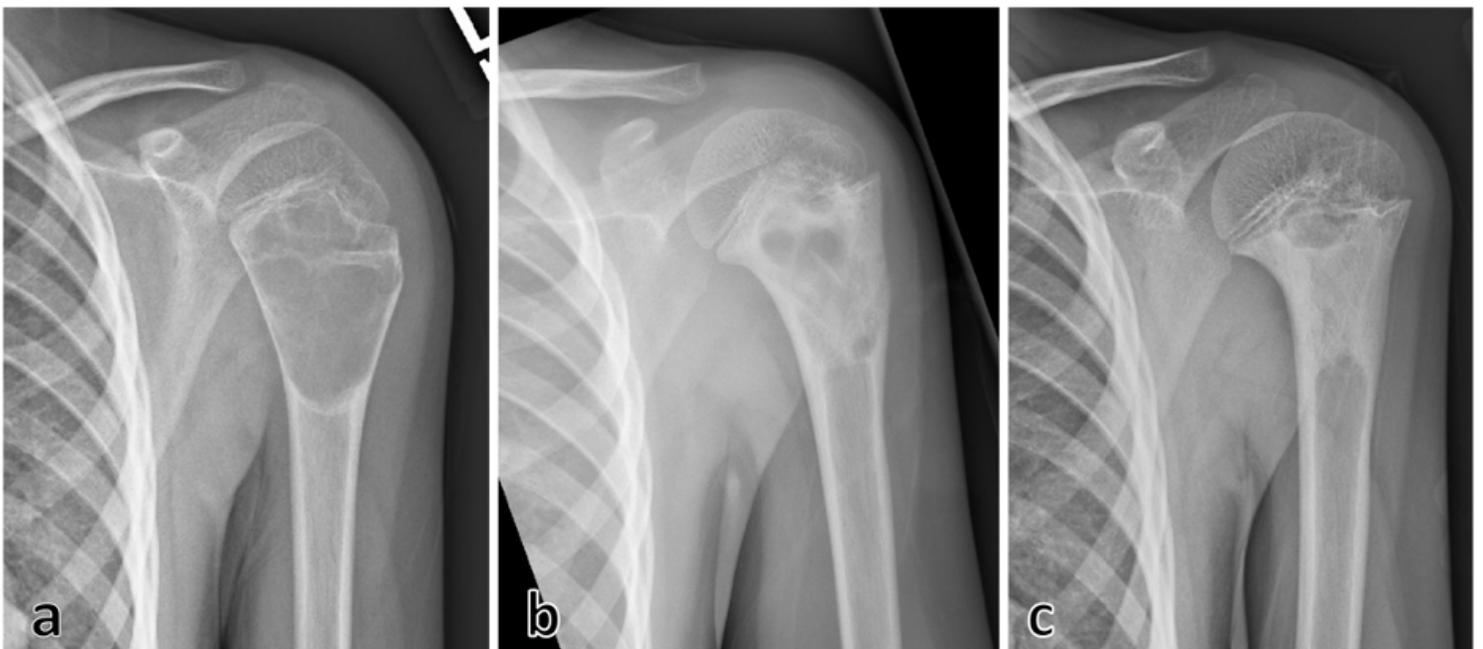


Figure 3

Consecutive left proximal humeral radiographs demonstrating consolidation of a UBC lesion taken at time points: a. 4 weeks after initial presentation (healed fracture line evident), b. 1.5 months after the first doxycycline injection, and c. 9 months after the second doxycycline injection (11 months after doxycycline initiation).

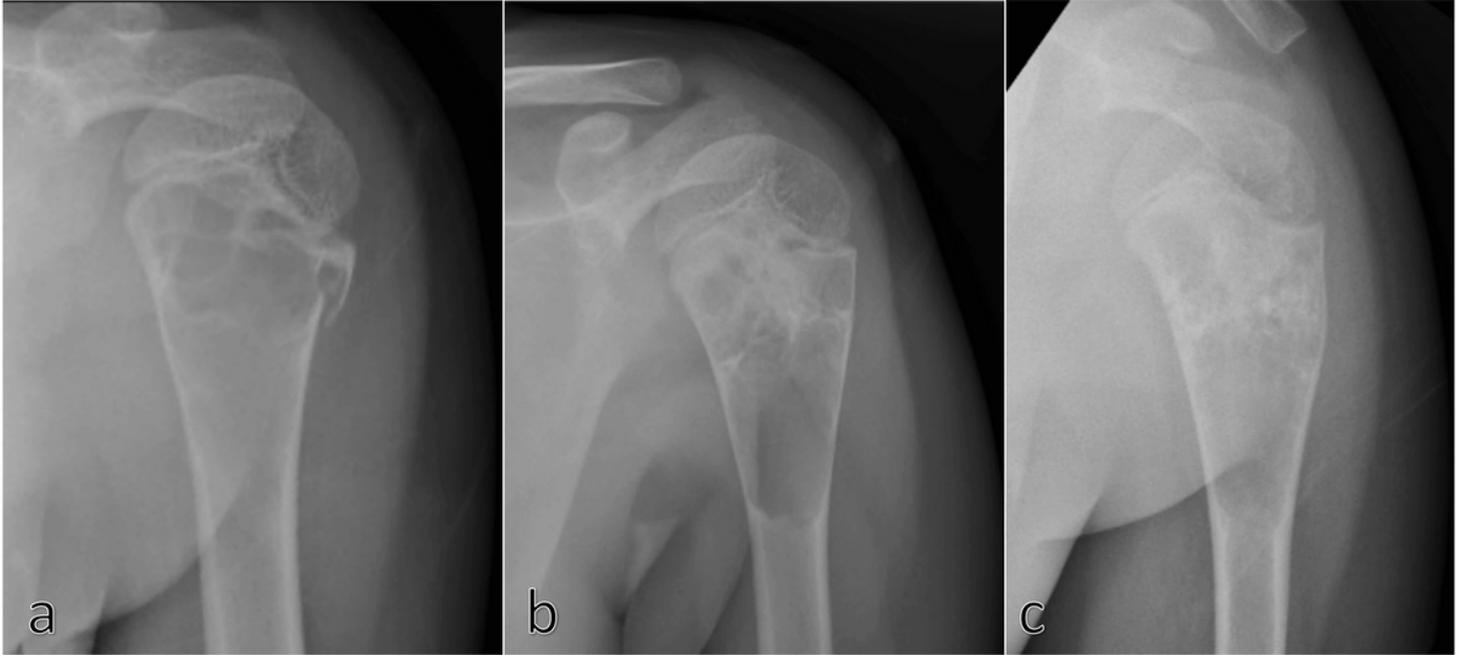


Figure 4

Consecutive left proximal humerus AP view radiographs. a. at first presentation with a pathologic fracture, b. 1 month prior to the first doxycycline injection with mature fracture callus present, and c. 2 months after the second doxycycline injection with increased cortical thickening and intralesional ossification.



Figure 5

Consecutive right pelvis radiographs demonstrating a UBC lesion taken at time points: a. 6 months prior to first doxycycline injection at the initial presentation with hip pain, b. 2 months prior to serial doxycycline injections when the pain recurred, and c. 2 months after third doxycycline injection (6 months after doxycycline initiation)



Figure 6

Consecutive right wrist radiographs demonstrating pathologic fracture followed by lesion ossification and ultimate resolution at time frames: a. 5 months prior to the first doxycycline injection at the initial presentation of the recurrent fracture, b. 2 months after the first injection, c. 2 months after the second doxycycline injection, and d. 9 months after the second doxycycline injection