Percutaneous Doxycycline Treatment of Juxtaphyseal Aneurysmal Bone Cysts

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Background: A recurrence rate of 19% to 23% has been reported in juxtaphyseal aneurysmal bone cysts (ABC) without en bloc resection or amputation. No percutaneous surgical techniques or drug treatments have demonstrated consistent bone healing with normal physeal growth and a recurrence rate of $<19\%$. Doxycycline has properties that may make it an appropriate agent for percutaneous treatment of juxtaphyseal ABC in skeletally immature patients.

Methods: We retrospectively reviewed 16 patients who underwent percutaneous treatment of ABCs with doxycycline from 2006 to 2011. The mean age was 7.1 years (range, 2 to 15 y). There were 16 treatment locations: humerus (9), tibia (3), fibula (2), femur (1), and ulna (1). Sixteen patients completed treatment involving 102 treatment sessions (2 to 14 sessions per patient). Treatment response was evaluated radiographically by measuring the lytic component, thickness of involved cortex, and signs of bony remodeling, and evidence of physeal growth arrest. Recurrence was indicated by new areas of lytic destruction after completion of treatment. The minimum follow-up was 18 months (mean, 39 mo).

Results: All 16 patients demonstrated reduction in lytic destruction, bony healing, and bony remodeling. One patient demonstrated recurrent minimal lytic destruction after 20 months of observation. Seven patients (7/16, 44%) demonstrated physeal ABC involvement; 5 of 7 patients healed with a physeal bone bridge, all $\leq 15\%$ of the physeal surface area, 1 with mild central physeal deformity. All patients with focal transphyseal ABC involvement (4/4, 100%) demonstrated focal bone bridge after treatment. No patient had diffuse physeal growth arrest; only patients with intraphyseal or transphyseal ABC involvement had focal physeal growth arrest.

Conclusions: In this series, patients undergoing percutaneous doxycycline treatment of juxtaphyseal ABCs demonstrated ABC healing and a recurrence rate of 6% at >18 months. Patients without physeal ABC involvement demonstrated no evidence of physeal growth arrest.

Level of Evidence: Level IV—therapeutic study.

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The authors declare no conflicts of interest.

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Aneurysmal bone cyst (ABC) is a benign bone neoplasm that can sometimes be difficult to treat without en bloc resection or amputation.[1–7] Traditional surgical techniques have reported wide-ranging recurrence rates of the disease, from 12% to 75%, with 90% detected within 2 years of surgery, including a 75% recurrence rate in children younger than 10 years old.[1–11] In skeletally immature patients, recurrence is associated with juxtaphyseal locations.[8–11] Juxtaphyseal ABC involvement has been reported to involve both the physis and epiphysis in 23% of patients, with growth disturbance in 55% following surgical treatment.[10] Alternatives to surgical treatment have been elusive. Percutaneous treatment has been attempted with ethibloc and polidocanol. Variable healing response rates have been reported from 58% to 94%, but with complications including pulmonary embolism, skin necrosis, pain, swelling, and fever.[12,13] Because of these complications, ethibloc is no longer used in treatment of ABC, and polidocanol is not approved for use in the United States.[4–14]

Upon histologic analysis, ABC consists of mesenchymal fibroproliferative stroma containing osteoclast-like giant cells and vascular spaces.[15–18] Specific translocational events are also commonly found on chromosomal bands 16q22 and 17p13 with TRE17/ubiquitin carboxyl-terminal hydrolase 6 (USP6) oncogene rearrangements found in primary ABCs.[18–26] The development of the ABC fibroproliferative stroma containing the upregulated osteoclast-like giant cells and prominent vascular spaces is promoted by the USP6 oncogene.[17,18,25] High levels of matrix metalloproteinases (MMP-9 and MMP-10), tartarate-resistant acid phosphatase, and cathepsin K are osteolytic characteristics of osteoclasts that are expressed in the multinucleated giant cells in ABCs.[18–26] High levels of vascular endothelial growth factor (VEGF) in addition to MMPs have also been reported to be expressed in ABCs and osteolytic lesions of the bone.[17,25,26] Similar to destructive processes associated with MMP production in bone malignancies, the aggressive bone destruction in ABCs is most frequently associated with TRE17/USP6 oncogene promotion and upregulation of MMP production.[25,27] In addition to MMP upregulation, TRE17/USP6

promotion further blocks osteoblastic maturation through an autocrine mechanism that involves bone morphogenic protein dysregulation.[28]

Doxycycline is a tetracycline antibiotic commonly used to treat a variety of infections, and has been approved by the US Food and Drug Administration since 1967. In addition to its antimicrobial action against bacteria, it has been demonstrated to heal microcystic and macrocystic lymphatic malformations (associated with elevated VEGF and MMPs).[29–32] Doxycycline demonstrates antitumoral properties with inhibition of MMP and angiogenesis in bone and soft-tissue malignancy cell cultures,[33,34] inhibits osteoclastic function, and induces osteoclastic apoptosis.[35–37] In addition, an animal study has shown that doxycycline can enhance osteogenic healing of bone defects.[38] The authors previously have reported pathologic specimens from 3 ABC patients treated with doxycycline injection 1 to 2 weeks before surgical resection with histologic evidence of tumor necrosis.[39]

Seventy-one patients have been treated for ABC in the authors' institution. The purpose of this study is to answer 5 questions regarding percutaneous treatment of juxtaphyseal ABC with doxycycline: (1) Is there reduction of lytic bony destruction and evidence of new bone healing? (2) Is there evidence of bony remodeling? (3) What is the recurrence rate after percutaneous treatment? (4) Is there evidence of physeal growth arrest after percutaneous treatment? and (5) Is physeal growth arrest with juxtaphyseal ABC predictable?

METHODS

We retrospectively reviewed 16 patients with juxtaphyseal ABC who underwent percutaneous treatment with doxycycline (off-label use) delivered in a protein foam delivery system from 2006 to 2011. The 16 patients in this study group were a subset of 71 patients who had undergone percutaneous doxycycline therapy for ABC in the spine, skull, flat bones, and long bones. The indications for injection treatment were: (1) recurrence after surgical curettage and grafting; (2) surgeon request for percutaneous treatment as an alternative to surgical treatment; and (3) patient request for percutaneous treatment. We treated ABCs of the humerus (9), tibia (3), fibula (2), ulna (1), and femur (1) in 102 sessions (mean, 6.4 sessions per patient; range, 2 to 14). Ages ranged from 2 to 15 years (mean, 7.1 y). All patients had diagnostic plain radiographs and 13 of 16 had preoperative MRI examinations. Seven of the patients demonstrated evidence of transphyseal involvement of the involved bone. All 16 patients had histologic diagnosis of ABC from either previous surgical biopsies (6) or core-needle biopsies (10). Pathologic diagnosis was confirmed with presence of fibroproliferative stroma, osteoclast-like giant cells, and vascular spaces. Posttreatment follow-up ranged from 24 to 67 months (mean, 42 mo).

Treatment procedures were carried out on an outpatient basis in the interventional radiology suite with general anesthesia or intravenous sedation. ABC percutaneous access with 14 to 25 G needles was performed with sonographic, fluoroscopic, or CT guidance. Needle size was determined by the integrity of overlying cortical bone and on the need for access for core biopsy. Small-gauge needles (20 to 25 G) were used for direct intraparenchymal tumor injections of doxycycline in the absence of bony cortex. Sonography[40] was used when there was either an absence of overlying bone or a rim of very thin cortical bone overlying. Contrast injection studies with fluoroscopy or CT were performed before the doxycycline injection. When contrast cystograms demonstrated considerable venous outflow, a tourniquet was applied to the extremity to maintain intraosseous delivery and decrease the potential for pulmonary embolism of doxycycline. Doxycycline (10 mg/mL) was used as the chemical ablation agent and delivered as a protein foam (mixture of doxycycline and 25% albumin and agitated with air to create a stable protein foam delivery system).[39] Doxycycline foam was injected into the cystic locules and, when possible, into the solid elements of the ABC. Postprocedural pain was managed with either oral NSAIDs or oral narcotic analgesics. Follow-up radiographs or CT/MRI studies were routinely performed at 6 to 10 weeks following respective treatments; subsequent treatment procedures were scheduled at 8- to 12-week intervals. Treatment was considered completed when either lytic areas were healed with new bone or small lytic areas remained stable after 2 consecutive treatments. Patients were informed of a minimum 5-year surveillance period after treatment to identify lucent foci that expand and demonstrate the need for further treatment. New areas of bony lysis (or expansion of lucent foci) during the surveillance period are regarded as recurrence, and were treated with further percutaneous doxycycline injections.

When treatment was completed, follow-up radiographs were performed every 6 months for 12 months and annually thereafter for 5 years (the minimum surveillance period was 2 y for inclusion in this study). Posttreatment MRI or CT studies were performed on patients with physeal deformity or suspected physeal growth arrest. Radiographic (or CT, MRI) imaging reviews and measurements were performed by 2 of the authors.

Images were evaluated for: (1) evidence of size volume reduction of prior lytic destructive ABC lesions, and bony healing of the ABC measured by thickening of involved bony cortex (cortex overlying the ABC measured from a single outer periosteal surface to the respective endosteal cortical surface); (2) evidence of bony remodeling (return of bone to metaphyseal concave contour as ABC volume shrinks) versus persistent convex bulbous deformity with healing; (3) evidence of recurrent bony osteolysis or an expansion during the follow-up surveillance; and (4) evidence of physeal growth arrest. Physeal arrest was measured by either focal or diffuse physeal arrest with bone bridge. Bone bridges were measured with the percentage of involved physeal surface area. In addition, involved physes and respective metaphyses were evaluated for radiographic evidence of deformity (Figs. 1–3).

We determined differences (measurement of lytic focus volume) in bony lytic regions before and after treatment by both the Shapiro-Wilk normality test and the 1-sample t test. We determined differences in bone

healing, specifically thickness of affected bony cortex, before and after treatment, by both the Shapiro-Wilk normality test and paired *t* test.

RESULTS

We observed a lesion volume reduction (posttreatment cyst volume compared with pretreatment volume) of the ABC lytic area in all 16 patients ($P < 0.001$) (Table 1). Sixteen of 16 patients demonstrated >95% bony healing that included new bone filling of the previous lytic destructive area and thickening of the affected cortex (posttreatment ABC cortical thickness compared with pretreatment cortical thickness; $P < 0.001$). All patients demonstrated bony remodeling of the involved sites, with conversion of outward convex metaphyses before treatment, to inward concave metaphyses following treatment. All patients have completed the percutaneous protocol. Nine patients underwent posttreatment CT or MRI evaluation. One patient (1/16, 6%) demonstrated a new focal area of bony lysis 20 months following completion of the initial treatment protocol. Seven of 16 (44%) demonstrated physeal ABC involvement (Table 2). Eleven of 16 (69%) patients demonstrated visible migration of the bony healing without evidence of physeal bar or deformity on x-ray, CT, or MRI. Five of 16 (31%) patients demonstrated focal physeal bone bridge on posttreatment CT or MRI, with only 1 patient demonstrating physeal/metaphyseal central

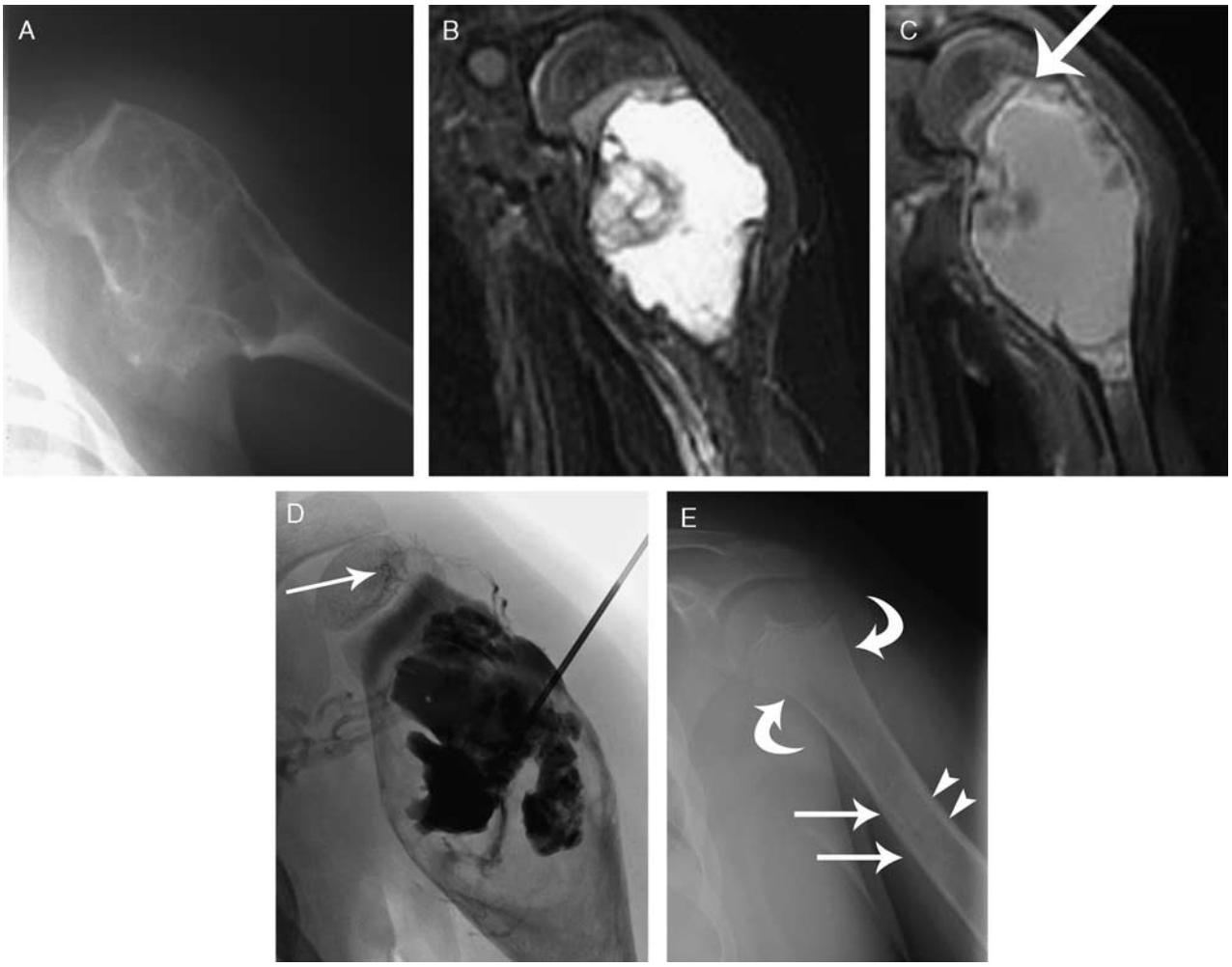

FIGURE 1. A 4-year-old male with left proximal humeral ABC with physeal involvement before treatment. A, Radiograph of the left humerus before percutaneous doxycycline treatment demonstrating lytic, expansile metaphyseal changes from the ABC. B, T2-weighted MRI demonstrates the extensive metaphyseal involvement of the multilocular ABC. C, Gadolinium-enhanced T1-weighted MRI demonstrates physeal, but no transphyseal involvement of the ABC (arrow). D, Fluoroscopically guided contrast injection before doxycycline injection demonstrates contrast filling the ABC cystic locules as well as normal transphyseal vascular channels (arrow). E, Radiograph of the left humerus 67 months following treatment demonstrates healing of the lytic destructive ABC foci (arrows) and cortical thickening in the healed ABC site (arrowheads), remodeling of the proximal humerus metaphysis with a concave metaphyseal waist (curved arrows), and distal migration of the healed ABC bony scar into the proximal humerus diaphysis (arrows), and no radiographic evidence of physeal growth disturbance or physeal bony bridge. ABC indicates aneurysmal bone cyst; MRI, magnetic resonance imaging.

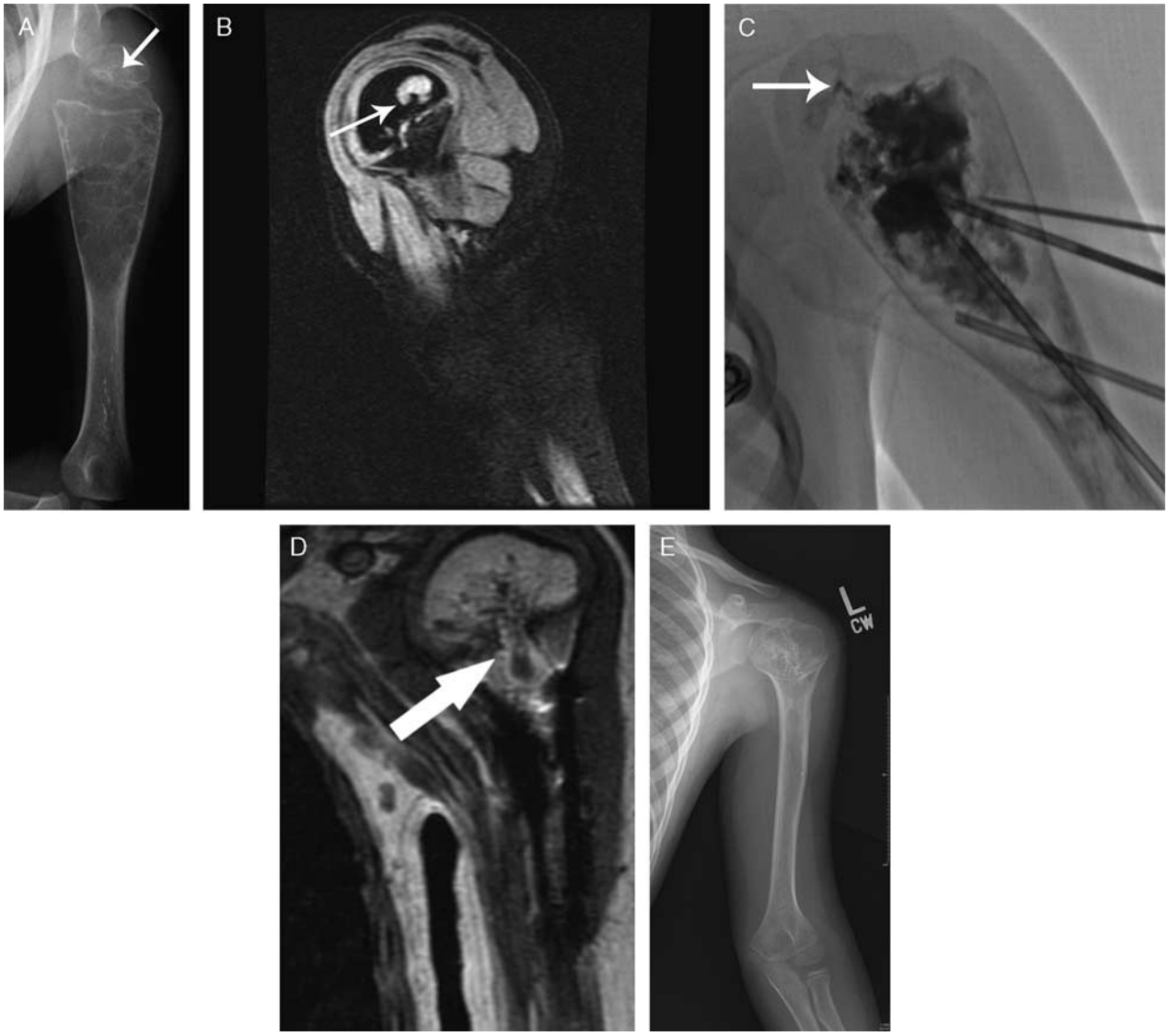

FIGURE 2. A 2-year-old male with left proximal humeral ABC with transphyseal involvement before treatment. A, Radiograph of the left humerus before percutaneous doxycycline treatment demonstrating epiphyseal lytic destruction from transphyseal invasion of the metaphyseal ABC (arrow). B, Sagittal T2-weighted MRI demonstrates the localized transphyseal involvement of the ABC (arrow). C, Fluoroscopically guided contrast injection before doxycycline injection demonstrates contrast filling the ABC cystic locules as well as the vascular channels of the localized transphyseal ABC tumor invasion (arrow). D, T1-weighted coronal MRI demonstrates the localized physeal growth disturbance and physeal bony bridge at the site of the healed transphyseal ABC involvement (arrow). E, Radiograph of the left humerus 45 months following treatment demonstrates healing of the lytic destructive ABC foci and cortical thickening in the healed ABC site, remodeling of the proximal humerus metaphysis with a concave metaphyseal waist and localized beak-like deformity in the physis localized to the site of healed transphyseal ABC involvement. ABC indicates aneurysmal bone cyst; MRI, magnetic resonance imaging.

inferior-beaked deformity in the proximal humerus. This bone bridge was noted only in 5 of 7 patients who had intraphyseal or transphyseal involvement with the ABC (4, humerus; 1, femur), notably in the same physeal locations identified on pretreatment imaging studies and confirmed during intralesional pretreatment contrast injections in 5 of 5 patients with physeal ABC involvement. The bone bridge constituted $\leq$15% surface area of the involved physes in all 5 patients. All patients (4/4) with transphyseal ABC involvement demonstrated focal bone bridge with healing of the ABC. No patients demonstrated diffuse physeal growth arrest. Physeal growth was symmetrical (across the width of the physis) and without deformity in 15/16 patients (94%); 1 patient demonstrated a central inferior-beaked physeal deformity of the involved proximal humerus that has not required treatment at this writing.

One case of focal skin necrosis (1 cm) was noted before utilization of a 2-needle cyst decompression technique during injection. This was presumed to be secondary to

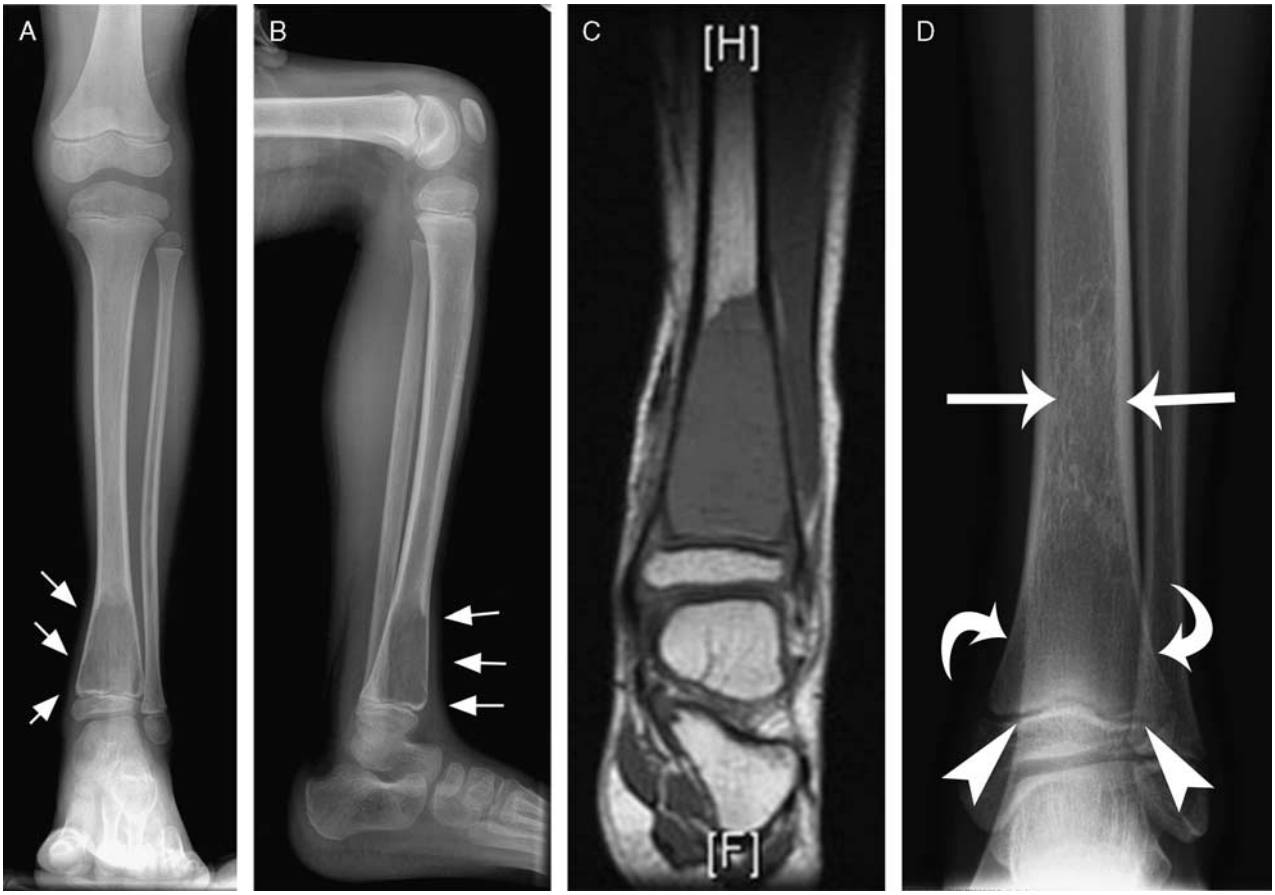

FIGURE 3. A 7-year-old boy with juxtaphyseal distal left tibial ABC with physeal involvement and no transphyseal invasion. Frontal (A) and lateral (B) radiographs of the left ankle demonstrate extensive metaphyseal juxtaphyseal ABC, with an expansile lytic area of bone destruction before treatment (arrows). C, T2-weighted coronal MRI demonstrates the extensive juxtaphyseal ABC with no transphyseal invasion. D, Anteroposterior left ankle radiograph 47 months following treatment demonstrates distal migration, cortical thickening, and healing of the lytic destructive ABC sites (arrows); in addition to return of the normal distal tibial metaphyseal concave morphology (curved arrows), and no evidence of physeal growth disturbance or deformity (arrowheads). ABC indicates aneurysmal bone cyst; MRI, magnetic resonance imaging.

TABLE 1. Patient Demographics

Patient	Age (y)	Site	No. Treatments	Doxycycline Dose (Range) (mg)	Pretreatment Lytic Volume (mL)	Posttreatment Lytic Volume (mL)	Pretreatment Cortical Thickness (mm)	Posttreatment Cortical Thickness (mm)	Follow-up (mo)
1	7	Tibia	6	100-600	25	0.02	1	7	47
2	11	Tibia	5	120-400	19.5	0.2	0.1	3	42
3	15	Humerus	8	120-560	45	12	1	7	35
4	7	Fibula	14	50-200	2	0.01	0.1	3.1	32
5	5	Femur	2	280-360	18	0.2	< 0.1	3	45
6	2	Humerus	11	80-400	34	0.7	1	6	45
7	10	Humerus	3	40-80	3	0.01	0.5	4	24
8	5	Humerus	5	40-100	39	0.3	1	4	30
9	7	Humerus	3	80-100	38	0.2	0.5	4	54
10	8	Humerus	3	80-400	48	No lytic areas	1	8	36
11	4	Humerus	4	205-800	111	1	0.5	6	47
12	11	Humerus	6	70-160	32	0.02	0.5	6	30
13	4	Humerus	13	40-500	39	0.01	< 0.1	4	34
14	6	Humerus	2	200 (twice)	10	0.4	1	3	53
15	3	Ulna	6	5-130	6	No lytic areas	0.2	3	58
16	6	Fibula	6	40-200	7	1.5	1	2	67

TABLE 2. Physeal ABC Involvement in 7 Patients

Age (y)	Site	No. Treatments	Physeal Arrest	Bone Bridge (mm)	Bone Bridge Percentage of Physeal Surface Area	Deformity
5	Proximal femur	2	Focal	2 × 3	0.5	None
12	Proximal tibia	5	None	None	—	None
15	Proximal humerus	9	Focal	10 × 14	5.3	None
2	Proximal humerus	14	Focal	6 × 14	8	Central inferior beak
10	Distal humerus	3	Focal	4.5 × 2.6	1.4	None
4	Proximal humerus	11	Focal	12 × 12	15	None
4	Proximal humerus	13	None	None	—	None

ABC indicates aneurysmal bone cyst.

overpressurization and extravasation of doxycycline. No complications of nerve injury,[41–43] infection, pulmonary embolus, or vascular thrombosis occurred. No patient had development of pathologic fracture during ongoing treatment. No patient required therapy to return to normal activities. Although oral and systemic doxycycline has long been associated with staining of the teeth in pediatric patients,[44,45] no staining was observed in our cohort.

DISCUSSION

ABCs are among the most aggressive benign bone neoplasms. The chromosomal translocation that triggers development of the USP6 oncogene results in subsequent development and upregulation of (1) destructive fibroproliferative stroma, (2) destructive osteoclast-like giant cells, (3) MMPs, and (4) VEGF.[18–26] This 4-fold combination of bony destructive components and growth of vascular spaces are all targeted by doxycycline for ABC healing.[38] Furthermore, doxycycline is known to promote osteogenesis in treated bone defects.[37] The purpose of this study is to answer 5 questions regarding percutaneous treatment of juxtaphyseal ABC with doxycycline: (1) Is there reduction of lytic bony destruction and evidence of new bone healing? (2) Is there evidence of bony remodeling? (3) What is the recurrence rate after percutaneous treatment? (4) Is there evidence of physeal growth arrest after percutaneous doxycycline treatment? and (5) Is physeal growth arrest with juxtaphyseal ABC predictable?

Limitations of this study include the following. First, the sample size is small. The patient group was selected from 71 patients with ABC treated with percutaneous doxycycline and represents the focused group of patients for evaluation of juxtaphyseal ABC who have a minimum of 18-month follow-up. ABCs involving physeal equivalent areas such as the ilium, spine, and scapula were not included in this sample. Second, this series is a single cohort study; the sample was not prospectively compared with treatment with high-speed burr, cryotherapy, or other surgical-chemical agent (phenol) adjunctive therapies. Third, cross-sectional imaging following treatment was performed in only 9 patients; plain radiographic evaluation may not detect small physeal bone bridges that are not associated with physeal growth deformities. Further studies will include routine pretreatment and posttreatment MRI imaging for more thorough follow-up evaluation. Fourth, 2 of the cases required 13 and 14 injections, respectively, and the burden to patients and families and the cost associated with multiple medical interventions must be a consideration in determining treatment. In straightforward cases that do not risk the physis and are relatively easy to access from an anatomic standpoint, intralesional curettage may be preferable in providing definitive treatment of ABC.[46,47]

The results of this study support both the effect of doxycycline to target ABC tumor reduction and bony healing. In addition to the recognized effects of doxycycline on giant cell function/apoptosis, MMP inhibition, and VEGF inhibition, our experience supports a primary effect of doxycycline on ABC stromal resulting in necrosis,[39] translating into reduced ABC tumor volume with healing as measured radiographically ($P < 0.001$). New bone growth with healing is documented with measurable regrowth cortical bone resorbed by the ABC ($P < 0.001$). This new bone growth is consistent with the known doxycycline stimulation of healing and osteogenesis.[38]

Remodeling of the metaphyses invaded and expanded by the ABC neoplastic cells provides optimism for clinicians during patient education, anticipating favorable outcomes following percutaneous doxycycline treatment of juxtaphyseal ABC. The fact that 100% of patients demonstrated reparative remodeling of metaphyses also suggests that in addition to inducing apoptosis of ABC neoplastic giant cells, at a minimum, the normal metaphyseal osteoclasts maintain function with the potential to remodel the juvenile metaphyseal waist after treatment of the expansile ABC neoplasm.

A juxtaphyseal ABC recurrence rate of 6% following percutaneous doxycycline treatment compares favorably with previously reported series with recurrence rates of 19% to 23%. These data suggest that the antineoplastic effects of doxycycline, both at the stromal and cellular level, are effectively delivered through percutaneous injection, penetrating the neoplastic ABC vascular spaces, as defined by pretreatment contrast injection. The authors believe that ABC recurrence, as a neoplasm, is a function of residual cells that were not effectively killed during the initial series of treatment sessions, hence the need to monitor the patients for a 5-year period, to detect growth of residual foci of ABC cells that grow to a detectable size for targeted treatment. Once residual (or recurrent) foci of ABC cells are detected, minimally invasive injection techniques can again be utilized

for targeted treatment, using image guidance for precision, either CT, US, and/or fluoroscopic guidance.

Physeal growth arrest appears to clearly be a function of the location of ABC neoplastic process. The fact that no cases of diffuse physeal growth arrest were demonstrated supports the safety of doxycycline foam in the treatment of juxtaphyseal ABC without physeal invasion. The correlation of pretreatment definition of transphyseal ABC invasion and posttreatment bone bridges in identical locations supports the notion that the bone bridge is indeed healing of the ABC focus within the physis, as opposed to physeal injury induced by doxycycline injection.

The risk predictability of physeal bone bridge with healing is supported by the consistent identification of the transphyseal ABC foci on pretreatment imaging and during contrast injections, with bone bridge formation in the same location with healing. This pretreatment information is important as clinicians provide patients with prospective risk estimates of physeal injury when treatment options are discussed and decisions are made. These data further support the need to perform pretreatment MRI tumor imaging, evaluating the diagnostic nature of the ABC and meticulously evaluating the patient for physeal and epiphyseal involvement. Furthermore, patients with pretreatment evidence of physeal invasion, at a minimum, should have posttreatment MRI or CT to define bone bridges, even if small, for complete posttreatment planning and decision making. Finally, physicians must recognize that telangiectatic osteogenic sarcoma can mimic ABC in radiographs,[48,49] and biopsy results are essential in guiding treatment.

The strength of the data in this study further drives our clinical decisions to recommend targeted percutaneous doxycycline treatment of ABC as a neoplasm, to include the belief that doxycycline is a safe percutaneously delivered drug for treatment of juxtaphyseal ABC, with and without physeal invasion.

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