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Case Report

Single dose intralesional doxycycline foam infusion promotes bone growth and resolution of an odontoid aneurysmal bone cyst

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ABSTRACT

Background: Aneurysmal bone cysts (ABCs) are locally invasive bone tumors that most commonly arise in long bone metaphyses, the vertebral column, and pelvis, often presenting in the second decade of life. ABCs can be treated with resection, radiation, arterial embolization, and intralesional curettage. More recently intralesional doxycycline foam injections, which appear to act through the inhibition of matrix metalloproteinases and angiogenesis, have been used successfully, although multiple treatments are often required with this approach.

Case Description: A 13-year-old male with an incidentally discovered ABC filling much of the odontoid process but not violating the native odontoid cortex was treated with a single intralesional doxycycline foam injection delivered through a transoral approach with an excellent radiographic result. After placing a Crowe-Davis retractor, a transoral exposure of the odontoid process was performed with neuronavigation guidance. A fluoroscopy-guided Jamshidi needle biopsy was performed and via the needle doxycycline foam (2 mL 50 mg/mL doxycycline, 2 mL 25% albumin, and 1 mL Isovue 370 mixed with 5 mL of air) was infused, filling the cystic cavities of the odontoid process. The patient tolerated the operation well. Two months postoperatively, a computed tomography (CT) scan demonstrated a decrease in the size of the lesion with substantial new bone formation. Repeat CT at 6 months showed no residual cystic lucency, formation of dense new bone, and only minimal irregularity of the cortex at the prior needle biopsy site.

Conclusion: This case illustrates that the use of doxycycline foam can be an excellent option when managing ABCs that cannot be resected without incurring significant morbidity.

Keywords: Aneurysmal bone cyst, Doxycycline, Minimally invasive neurosurgery (MIN)

INTRODUCTION

Aneurysmal bone cysts (ABCs) are benign but locally invasive tumors that have been observed in most bones but most often arise in the long bone metaphyses, spinal column, and pelvis during the first two decades of life.^[10] On imaging ABCs appear on radiographs and computed tomography (CT) as lucent bone lesions with thin-walled cavities and magnetic resonance imaging (MRI) generally demonstrates characteristic fluid-fluid levels within cystic cavities of the lesion. While the etiology of ABCs has been historically poorly understood with a longstanding hypothesis that these were reactive lesions arising in the setting of a localized vascular

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disturbance, recent data have shed light on the neoplastic origins of ABCs. Specifically, rearrangements of t(16:17) found in 69% of ABC's place cadherin-11 in control of the protease 6 oncogene and induce matrix metalloproteinase (MMP) production resulting in tumorigenesis.^[12,26] Growth of the lesion exerts pressure from within the bony matrix resulting in sclerosis and bone remodeling, leaving behind a cystic, hemorrhagic cavity.^[3]

The current treatment modalities include combinations of en bloc resection, intralesional curettage with or without bone grafting, endovascular arterial embolization, and radiation.^[15] However, for cervical spine lesions, surgical approaches such as curettage and en bloc resection are associated with high morbidity often necessitate fusion for spinal stability.^[13] Recently, minimally invasive techniques aimed at controlling bony remodeling have been attempted to alleviate this burden. Regimens include multiple injections of percutaneous sclerotherapy (polidocanol and Ethibloc) and doxycycline mixtures.^[1,16,20] Due to a high frequency of major local and systemic complications, the use of Ethibloc has been largely abandoned, and polidocanol is not approved for use in the United States.^[9,20,22] First reported in a 2013 retrospective study, doxycycline was found to significantly decrease lytic destruction and promote bone healing through antagonism of proangiogenic factors such as MMPs and vascular endothelial growth factor [VEGF].^[20] However, in a number of case reports and small series on this issue, the authors found that more than one treatment of the lesion with doxycycline-albumin foam was necessary to achieve ABC obliteration and complete bone remodeling.^[5,7,19,20,24] We present a case of a patient with an odontoid ABC who achieved complete resolution of the ABC with complete ingrowth of new bone in 6 months following a single injection of a doxycycline-albumin foam.

CASE REPORT/CASE PRESENTATION

A 13-year-old male with a history of prematurity, meningococcal meningitis with post-meningitic neuropathic pain, tics, and staring spells concerning for seizures presented after being struck by a car while riding his bicycle. Polytrauma imaging workup revealed an incidentally discovered odontoid process cystic lesion [Figure 1] with internal fluid-fluid levels on MRI consistent with ABC [Figure 2]. Post-contrast MRI did not reveal any enhancing mass(es) in association with the cystic odontoid process lesion to raise concern for this lesion representing a secondary ABC arising in the context of a preexisting neoplastic process such as giant cell tumor, chondroblastoma, osteoblastoma, or osteosarcoma.

The patient was allowed to make full recovery from his traumatic injuries prior to embarking on the management of the ABC. The indication for surgical intervention was primarily the location of the lesion. Any progression of



Figure 1: Incidental finding of cystic mass of the odontoid process on initial computed tomography, (a) coronal view, (b) sagittal view.

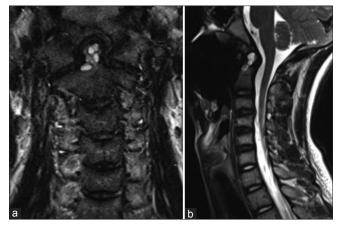


Figure 2: T2-weighted magnetic resonance imaging demonstrating fluid-fluid levels of odontoid process cyst, highly suspicious for an aneurysmal bone cyst, (a) coronal view, (b) sagittal view.

the lesion could potentially affect cervical stability given the role of the odontoid process in neck range of motion biomechanics. Invasive intervention was decided upon to limit the chance that this ABC will expand and erode through the outer cortex of the odontoid process. The alternative option proposed would be conservative management with serial imaging or non-invasive therapies such as radiation.

A preoperative angiogram was performed 10 weeks after first discharge from the hospital for two reasons. The first reason was to evaluate the vasculature of the ABC and potentially embolize the main arterial feeders. The second reason was to confirm resolution of the previously noted traumatic right transverse/sigmoid sinus thrombosis. The diagnostic query failed to show any identifiable target for ABC embolization. However, there was confirmation of good flow with no residual clot in the right transverse/sigmoid sinus. The surgery was performed 2 days after the diagnostic use of intraoperative angiogram. There was the neuronavigation (Stealth S8 AxiEM system) and intraoperative fluoroscopy. The patient was supine on a standard operating room table and his head was aligned in a neutral position on a horseshoe head holder. The operative exposure was performed by our otolaryngology colleagues. A Crowe-Davis mouth gag was placed. Two red rubber catheters were placed through the mouth and nose to elevate the palate. The posterior oropharynx was exposed, C1 arch was palpable and confirmed with navigation. A midline vertical incision was made in the posterior oropharynx. Dissection was then taken through the mucosa, muscles, and vertically through the anterior longitudinal ligament to expose the arch of C1 and then carried slightly inferiorly to expose the base of the ventral odontoid and cephalad aspect of the ventral C2 body.

With the anterior aspect of C2 exposed, a Jamshidi bone biopsy needle was used to enter the cortical bone at the anterior aspect of C2, near the base of the odontoid process under direct fluoroscopic guidance. A core sample of tissue from within the odontoid lesion was removed for permanent pathology. When the Jamshidi needle was withdrawn from C2, egress of dark (chronic) blood products was noted from the hole left in C2 by the needle pass.

Next, a doxycycline-albumin foam was created using the protocol first described by Shiels and Mayerson,^[20] albeit with the addition of Isovue 370 for better fluoroscopic visualization of foam infusion. Specifically, doxycycline (2 mL of 50 mg/mL concentration), albumin (2 mL of 25% human serum albumin), and Isovue370 (1 mL) were sterilely mixed with 5 mL of air by flushing the mixture back and forth between two Luer lock syringes with an interposed stop cock numerous times. At the conclusion of the mixing process, 10 cc of the doxycycline/albumin/Isovue370 foam was maintained in a single sterile 10 cc syringe. This syringe containing the doxycycline/albumin/Isovue370 foam was connected to the Jamshidi needle using a Luer lock adapter. The Jamshidi needle was then inserted through the C2 bone defect made previously under direct fluoroscopic guidance. Once in position, the doxycycline/albumin/Isovue370 foam was infused into the cystic cavities of the odontoid lesion under direct fluoroscopic guidance. Complete filling of the lesion was appreciated. At this point, the needle was withdrawn, and the resulting hole left was plugged with a small piece of Gelfoam to prevent egress of the doxycycline/ albumin/Isovue370 foam.

The otolaryngology team commenced with a multilayer closure after adequate hemostasis was obtained. The patient tolerated the procedure well. There were no postoperative complications, and he was discharged the next day. 2-month postoperatively, a CT scan demonstrated a decrease in the size of the lesion with substantial new bone formation [Figure 3]. A repeat CT at 6 months showed no residual cystic lucency, formation of dense new bone, and only minimal irregularity of the cortex at the prior needle biopsy site [Figure 4].

DISCUSSION

This case demonstrates a unique case of a single dose of doxycycline foam resulting in complete radiographic resolution of an ABC cystic cavity by 6 months following the initial procedure.

This patient's case was ideal for a minimally invasive treatment option given the location of the cystic cavity. Gross total resection of the odontoid would have unequivocally



Figure 3: Two-month post-operative computed tomography demonstrating resolution of the cystic cavity of the odontoid process, (a) coronal view, (b) sagittal view.

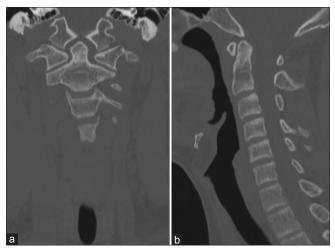


Figure 4: Six-month postoperative computed tomography demonstrating continued bony resolution of the cystic cavity, (a) coronal view, (b) sagittal view.

resulted in spinal instability and necessitated occipitocervical fusion, thus increasing morbidity and permanently reducing this young patient's neck range of motion. Also, at initial diagnosis and subsequent treatment, the lesion had not yet expanded to the point of violating the cortex of the odontoid. This allowed for the lesion to be completely filled with doxycycline foam within the confines of native cortical bone, which may explain why our patient's ABC responded so well to a single doxycycline treatment. A large exophytic component extending well away from the confines of the bone of origin may have precluded the excellent result we obtained.

ABCs often occur in long bones such as the femur, tibia, and humerus followed by the spine, pelvis, and small bones of the hand and feet.^[8] In the pediatric population, the most common spinal locations are the lumbar followed by the cervical spine.^[17] Solid enhancing soft tissue components on MRI in the context of ABC-like cystic bone changes may indicate malignant pathology with "secondary" ABC and should warrant more invasive resection for diagnosis and management. Even in the absence of malignant features on imaging en bloc resection is generally recommended when feasible for large lesions that present with neurological defects or instability.^[13,14,17] Compared with en bloc resection intralesional resection (curettage and/or high-speed burring) is associated with higher recurrence rates but the use of bone grafting or cement following intralesional resection does appear to reduce recurrence rates when intralesional resection is performed.[15,18] Arterial embolization and radiation therapy have been described as appropriate treatment modalities, with radiation therapy usually reserved for unresectable, aggressive, and/or recurrent ABCs.^[11]

Recurrence of ABCs is common after treatment, and some patient-related factors may contribute to the risk of recurrence. In a retrospective cohort of 53 patients with a median age of 14 years with primary ABCs, the authors found proximity to an open physis and age <12 years associated with a higher risk of recurrence following curettage of the lesion over a 24-month follow-up.^[6]

Reported recurrence rates of ABC following various treatment modalities are diverse. In a single-center, retrospective review of ABC management, recurrence rates were found to be 38.2% for intralesional curettage and 25% for en bloc resection. 90.6% of ABCs treated with percutaneous instillation of sclerotherapy (polidocanol) had no recurrence but demonstrated persistent disease.^[4] Of note, this patient cohort contained only six patients with spinal lesions, none of which underwent percutaneous instillation techniques. A prospective, randomized, unblinded study of 94 young-adult patients with primary ABCs found no significant difference in rates of radiographic healing when comparing surgical excision with bone grafting and

sclerotherapy (polidocanol) injection treatment groups, with high success rates of 84.8% and 93.3%, respectively, reported. However, the authors did note poorer functional outcomes and higher morbidity within the surgical excision cohort and an increased number of treatments were needed in the sclerotherapy cohort (mean, 2.3; median, 2; range, 1-5) as compared to the surgical cohort (mean, 1.2; range, 1-3).^[23] Lesional curettage with a combination of either allograft bone with ethyl methacrylate cement has been associated with an ABC recurrence of 20%, and cervical spine specific recurrence rate of 33%.^[8] In a recent systematic review of 28 manuscripts published between 2000 and 2020 the treatment failure/recurrence rates were similar when comparing the 594 patients treated with open surgical interventions to the 387 patients treated with injection therapy (polidocanol most commonly; doxycycline represented only 4% of the injection therapies delivered) at 14.4% and 14.7%, respectively, with rates of treatment failure/recurrence varying widely across individual studies (range: 0 - 40%).^[2]

The literature on the use of doxycycline foam in the treatment of ABCs is far more limited and, although existing reports suggest promising efficacy, outstanding questions remain about the appropriate timeframe to obtain follow up imaging and perform repeat doxycycline treatments in the setting of residual disease. The first report of doxycycline foam (10 mg/ mL of doxycycline mixed with 25% albumin and air) for the treatment of ABCs was published in 2013.^[20] In this study, 20 patients received a mean of five percutaneous doxycycline treatments (range: 2-14). These patients were evaluated 6 weeks after the initial therapy and those with incomplete healing of lytic areas were subject to further injections 2 weeks later.^[20] A retrospective review of the data for these patients undergoing multiple percutaneous doxycycline treatments found the recurrence rate of ABCs to be 6% at 18 months and 5% at 24 months.^[19,20]

In another retrospective and cohort study, it is suggested that a single injection of doxycycline foam followed by a waiting period of 12 weeks may be an appropriate timeline to assess for radiographic changes.^[25] The interval of time between initial injection and follow-up imaging is unclear, and should be further investigated to understand the time course of disease resolution.

Certainly, the case presented in this manuscript provides evidence that ongoing bone healing is possible between months 2 and 6 after doxycycline foam without repeat injections. Similar ongoing "late" healing after a single doxycycline treatment was also reported by Doyle et al who used doxycycline foam to successfully treat a recurrent ABC with a single treatment. They reported the case of a 12-year-old female who presented with neck pain found to have a large second and third cervical vertebral ABC for which she underwent resection and iliac crest bone grafting from C2 to C4. Six-month follow-up demonstrated cystic recurrence proximal to the iliac graft site and she underwent posterior-fusion occiput to C5 with iliac bone graft removal. Five months following the second operation, she was found to have a second recurrence, and at this time underwent intralesional doxycycline foam injection. A follow-up CT scan at 6 weeks demonstrated early bone formation and at 7 months, there was an extensive filling of the cavities with new bone.^[5]

Small case series have thus far suggested that recurrence rates following doxycycline foam injection are comparable to surgical resection. A case series of seven children with ABCs located in either the spine, pelvis, or femur, found six of the seven patients to have clinical and imaging signs of improvement after a single doxycycline-albumin foam injection.^[25] However, three of these seven patients ultimately received two doxycycline treatments. One of the patients in this seven-patient cohort progressed to surgery following the persistence of symptoms.

One study has retrospectively compared doxycycline foam to open surgical resection. Liu et al. compared 14 patients treated with multiple injections of doxycycline foam with 11 patients treated with open surgery for spinal ABCs. The doxycycline foam injection group had significantly decreased lesion size after the injections for the 24-month follow-up period, improvement in neurologic symptoms when present, and improvement in pain ratings on the visual analog scale (VAS).^[7] The authors found no difference in the rate of recurrence, post-procedural complications, or VAS score changes following either treatment modality. As the authors note, the sample size was small, and the data set was subject to confounding variables. Given the rare nature of ABC pathology and the novelty of doxycycline foam injections, prospective and randomized controlled trials are lacking in the literature.

A recent systematic meta-analysis on the management of juvenile bone cysts and ABCs reached the conclusion that surgical intervention was the most effective treatment; although, there were variations in success rates depending on the specific surgical approach employed. However, given that doxycycline injection and surgical excision both had high rates of success with 98% healing in both groups and 11% and 6% recurrence rates, respectively, the authors acknowledged that doxycycline injection remains a reasonable alternative. Importantly, the primary reason that the authors did not favor doxycycline injection as a first line treatment in cases without neurovascular compromise or structure instability was related to the frequent need for repeat doxycycline treatments to achieve complete bone healing in the published literature to date.^[21] Therefore, we felt that the case presented in this report serves to counter the notion that multiple injections of doxycycline are needed in all cases. Our case

also raises the question of whether some repeat injections in prior reports performed at early time intervals following the first treatment were necessary given the continued bone healing observed in our case between 2 and 6 months without intervening interventions.

Thus, given an excellent safety profile from existing literature, suggestion of efficacy that is at least on par with open surgical approaches, and the reduced morbidity and hospital length of stay that can be realized by avoiding upfront open resective surgical procedures the authors assert that doxycycline foam injections should be strongly considered in the management of newly diagnosed ABCs that are not associated with frank biomechanical instability or compression of neurovascular elements, particularly when it is feasible to deliver doxycycline foam treatment via a minimally invasive image guided percutaneous approach and in instances when a resective procedure is likely to be associated with morbidity.

CONCLUSION

We describe a case of odontoid ABC treatment with single intralesional doxycycline foam injection with excellent recovery and new bone formation. For patients where ABC resection is not feasible or would be associated with morbidity, doxycycline foam injections may be an effective and less morbid treatment option, particularly when it is feasible to deliver doxycycline foam treatment through a minimally invasive image guided percutaneous approach. While randomized controlled trials comparing doxycycline foam injections to open surgery are lacking, this case report adds to the growing body of literature around the excellent safety profile of this approach and highlights the fact that bone remodeling/healing can continue for months after a single doxycycline treatment.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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