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SCIENTIFIC ARTICLE

Aneurysmal bone cyst treated with percutaneous doxycycline: is a single treatment sufficient?

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Abstract

Objective The purpose of this case series is to report on the effectiveness of a single percutaneous injection of doxycycline as a primary treatment for aneurysmal bone cyst (ABC).

Materials and methods A retrospective cohort study was conducted on seven patients diagnosed with ABC at various anatomical sites, with the intention to treat by a single percutaneous injection of doxycycline. Mean patient age was 14 years.

Results Signs of treatment response were seen in six of seven patients after one injection. Three of the seven received a second treatment, despite signs of response. Another had expansion of the lesion after treatment, requiring excision. In total, three patients had a single injection of doxycycline as their sole treatment and another three showed signs of response after a single injection.

Conclusions A single percutaneous injection of doxycycline should be considered a viable primary treatment option for ABC.

Keywords Neoplasms · Tumor · Bone cysts · Aneurysmal · Treatment · Doxycycline · Intervention · CT guidance

Introduction

The World Health Organization defines aneurysmal bone cyst (ABC) as "A destructive, expansile, benign neoplasm of bone composed of multilocular blood-filled cystic spaces" [1].

ABC was first reported between 1942 and 1957 [2, 3]. The name originated from its appearance as a "ballooned-out" distension of the periosteum, similar to an aneurysm [4]. However, this name is a misnomer as the lesions lack an endothelial wall and are neither aneurysmal nor cystic [5].

ABC pathogenesis was initially thought to be caused by an increase in venous pressure leading to dilation and engorgement of the vascular bed within the cystic area in the bone [3, 6]. More recently, a neoplastic pathogenesis was implicated as nearly 70% of primary ABC lesions had translocation of chromosomal bands 17p13 with TRE17/ubiquitin carboxyl-terminal hydrolase 6 (USP6) rearrangements [7]. TRE17 blocks osteoblastic maturation via dysregulation of autocrine signaling of bone morphogenetic protein (BMP) [8]. The multinucleated giant cells in ABC induce expression of metalloproteinases (MMPs) −9 and − 10 [9] and vascular endothelial growth factor (VEGF) [10]. MMPs promote neoplasia by degradation of extracellular matrix and promoting angiogenesis [11]. The underlying (although unproven) basis of injection treatment is to inhibit MMP and angiogenesis. Doxycycline has antitumoral properties as outlined in the paper by Shiels et al. [12].

Optimal ABC treatment remains uncertain. Wide en bloc resection has excellent local control but is associated with high complication rates and is not always anatomically feasible [13]. More non-invasive methods include curettage with bone grafting, but this has a recurrence rate of 26% (12–59%) without adjuvants [14]. Minimally invasive surgical techniques have been proposed when it was observed that ABCs can heal after a pathological fracture or open biopsy [13]. This method was found to be 81% successful [15]. Other non-surgical treatment methods include: percutaneous sclerotherapy, embolization, radiotherapy, and medical treatment [13]. Embolization has high complication rates, radiotherapy is complicated by

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secondary malignancy and a high failure rate, and medical treatment is still in its infancy and not well established [13].

Sclerotherapy is considered first line, as it has a success rate of over 90% with low complication rates [13]. The most popular agent of choice is polidocanol, which treated all 72 patients (46 males) in one study [16] and had similar success rates in other studies [17, 18]. Polidocanol is variably available for osseous injection; the reported complications are minor, including local inflammatory reaction and hypopigmentation [16–18]. Bone marrow injection is also successful in most patients [19] but the process involved is relatively complicated.

Percutaneous doxycycline was shown to be effective in a single preliminary case series of 20 patients, with only one patient suffering a recurrence [12]. A case was previously reported of a 12-year-old patient with a recurrent ABC in the cervical spine successfully treated with doxycycline [20].

The purpose of this case series is to report on the effectiveness of a single percutaneous injection of doxycycline as a treatment for aneurysmal bone cyst.

Methods

A retrospective cohort study was conducted between November 2013 and June 2017 on eight patients diagnosed with ABC at various anatomical sites in whom the intention was to treat using percutaneous doxycycline. Because the study involved review of existing clinical information by the treating clinicians, specific ethics approval was not required. The clinical presentation, diagnostic investigations, procedure technique, and both clinical and imaging outcomes were reviewed. The length of anesthetic was derived from the anesthetic records. The radiation dose was obtained from the CT or fluoroscopy machine readout for the procedure.

One 26-year-old with an ABC in the C2 vertebra previously subject to needle and open biopsy underwent planning CT, which showed signs of early healing. Injection was not performed and the lesion went on to heal spontaneously. This patient is excluded from analysis.

A summary of the remaining seven is presented in Table 1. Indications for treatment included: (1) recurrence after surgery ($n = 1$); or (2) as an alternative to surgery suggested by either the surgeon or patient ($n = 6$). Patient 1 was contraindicated for surgery due to complications from two previous surgeries and recurrence of the ABC lesion, outlined in a previous case report [20]. The age range was 8 to 18 years (mean = 12 years). Diagnostic imaging included plain radiographs and computed tomography (CT) in all patients, and magnetic resonance imaging (MRI) in all but one patient. Histological examination in three patients was done either by surgical ($n = 1$) or core needle biopsy ($n = 2$). Diagnostic histological features included: multiple spindle septa surrounding hemorrhagic areas, giant cell-like osteoclasts, fibromyxoid stroma, inflammatory cells, and a USP6 rearrangement [21]. In the other four patients, the diagnosis was established on the basis of typical features on radiograph, CT and MRI, with no evidence of any other underlying process. All patients, therefore, had primary ABCs.

All patients presented with pain and four had a pathological fracture. Patient 3 also had sciatica from pressure on the S1 nerve roots. Post-procedure follow-up CT was performed in six patients and radiography alone in one. Healing was defined as development of intralesional mineralization in previously lytic areas, volume reduction in lesions, cortical thickening, bony remodeling, and healing of any pathological fracture. Non-healing was defined as osteolysis or expansion of the cystic area.

Technique of injection

Informed consent was obtained. A single radiologist performed each of the initial injections. Procedures were performed in the outpatient unit in radiology with general anesthetic ($n = 6$) or intravenous sedation ($n = 1$). Under CT ($n = 6$) or fluoroscopic ($n = 1$) guidance, all affected cysts were identified and entered with two 22-gauge spinal needles, following infiltration of 3–10 ml of local anesthetic. Intralesional injection was confirmed with 0.1–0.5 cc of iodinated contrast agent (Omnipaque-300, GE Healthcare, Buckinghamshire, UK).

Following that, a dose of doxycycline (Table 1) was injected in an air foam suspension with 5 ml albumin 20% [12]. Repeated injections were made into each lesion using the same 10-cc syringes, draining excess foam out through the second of the two needles. The needles were repositioned if required. In most cases, all parts of the lesions were seen to communicate, enabling complete coverage using one set of needle positions. At the end of the procedure, images confirmed that the cysts were mostly filled with aerated doxycycline suspension.

Results

Anesthetic times for the initial injection averaged 55 min (range, 45–90). The second injections took longer (average 90 min, range, 70–120). Radiation doses for CT averaged 380 mGycm (44–1064) for the initial injection and 404 mGycm (113–695) for the second. For fluoroscopy, the dose was 0.571 mGy.

CT scan post-treatment was done in six patients to assess the lesions. The first scan was at intervals of from 4 to 8 weeks post-procedure (average 5.7). The shortest interval was in patient 1, in whom the 4 week CT showed only very subtle blurring of the internal margins of the cysts but the 12-week CT showed definite signs of healing. In all five others, the first CT postprocedure showed definite signs of healing. One patient had radiographic follow-up at 12 weeks, without CT.

Table 1 Patient, lesion and treatment details

Patient number	Age (years)	Site	Pathological fracture?	Imaging	Biopsy	Treatment number	Doxycycline dose (mg)	Follow-up (months)
1	12	Cervical	Y	XR, CT, MRI	Y	1	400	60
2	14	Lumbar		XR, CT, MRI		2	400	24
3	11	Sacrum	Y	XR, CT, MRI	Y	2	400	21
4	18	Cervical		XR, CT, MRI	Y	1	300	Proceeded to surgery
5	15	Pelvis		XR, CT, MRI		2	400	14
6	8	Femur	Y	XR, CT, MRI		1	200	16
7	9	Femur	Y	XR, CT		1	400	18

After one treatment, signs of clinical and imaging improvement were seen in six of seven patients. Three patients received a single treatment and three received two treatments. In these six responders, follow-up has now been performed over periods of 14–60 months (average, 26 months), with no sign of recurrence.

One patient continued to experience pain and further extension of the lesion into the cervical lamina, prompting a surgical decision to excise the tumor. None of the patients experienced any complications from the doxycycline treatment.

Patients 2, 3, and 5 received two rounds of treatment (Table 1). Patient 2 received her treatments just under 14 months apart. The patient was asymptomatic and the lesion showed signs of healing (Fig. 1). The second treatment was performed at another center, at insistence from the patient's parents and against the advice of the primary radiologist. Patient 3 received her treatments 6 months apart. The indication was that there were concerns on her CT/MRI regarding an area that remained cystic with corticated margins, despite overall healing of the lesion and improved symptoms. On her most recent MRI, 21 months after her first injection, there remained a small cystic component despite overall improvement (Fig. 2). Patient 5 received his injections 3 months apart. The indication for the second was that his initial pain symptoms remained unchanged after the first procedure, despite evidence of bony healing on imaging. The second injection proved difficult due to an increase in cortical thickness and a partial ossified septum between lesion cavities, showing that the lesion was healing. His most recent CT, 14 months after his first injection, showed increased healing and he is currently pain-free and back to normal activities (Fig. 3).

Patient 4 was the only one who did not have a desirable response to doxycycline treatment. He was the only patient where the procedure was done under IV sedation (1.5 mg midazolam and 200 mcg fentanyl), because of lack of

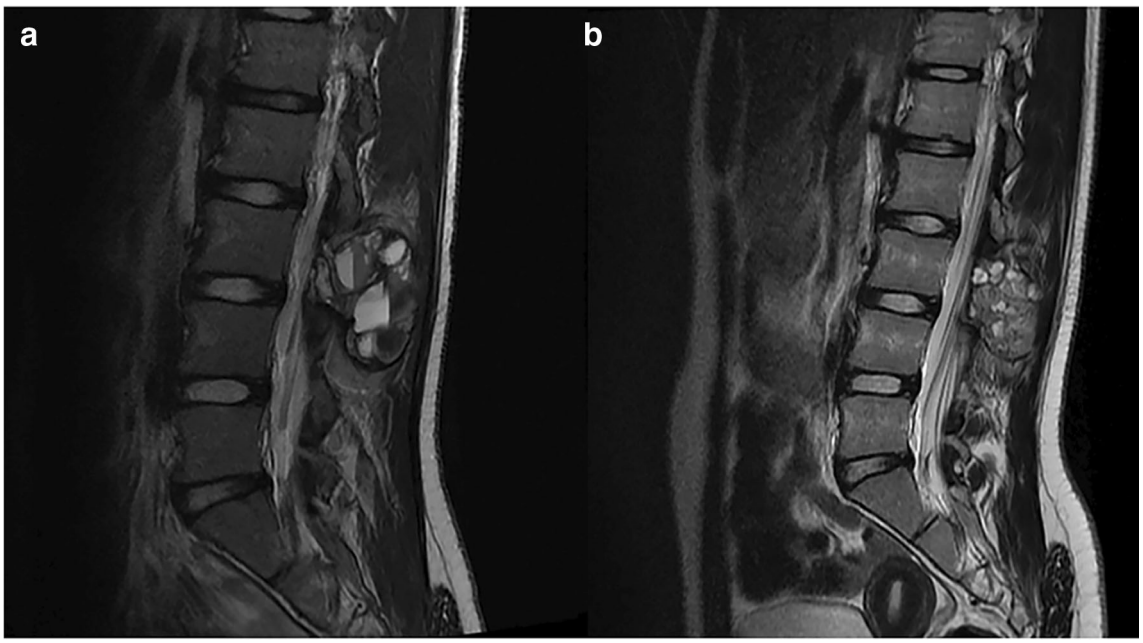

Fig. 1 Patient 2. Sagittal plane MR image of a 14-year-old female with an ABC of the lumbar spine treated with percutaneous doxycycline. **a** Pre-procedure; **b** 20 months post-procedure showing decrease in size and extent of fluid levels

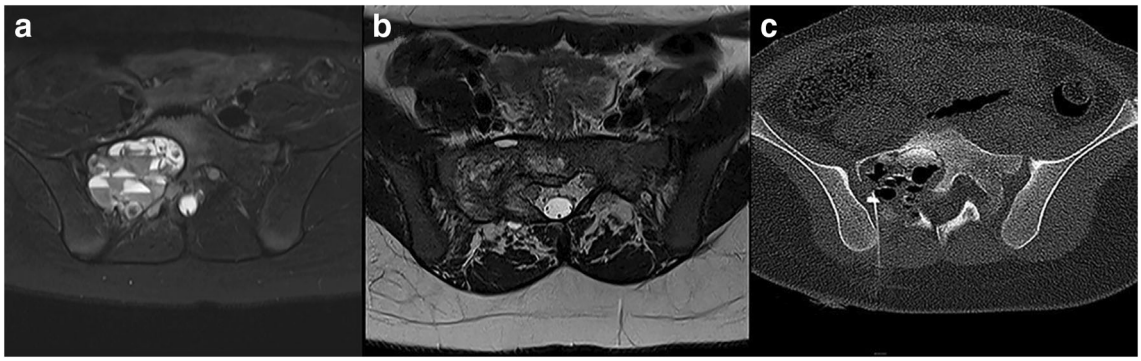

Fig. 2 Patient 3. Axial plane imaging of an 11-year-old female with an ABC of the sacrum treated with percutaneous doxycycline. **a** MR pre-procedure; **b** MR 19-month post-procedure demonstrating decrease in size, fluid levels, and displacement of right S1 nerve roots; **c** CT peri-procedure showing needle in locule and high-density injected material mixed with air formed from the aerated foam suspension

availability of an anesthetist. The procedure was uncomfortable for the patient due to aching pain. A total doxycycline dose of 300 mg was injected, and the radiologist had to stop due to patient discomfort. After a week post-procedure, he was complaining of on-going discomfort and pain when lying at night. CT scan showed increased size of the lesion with progressive involvement of the laminae. He subsequently went on to have an en block excision of the tumor. The excised tissue did show signs of healing response, containing dense trabecular hyalinized areas with "chicken wire" calcification. His most recent MRI, 24 months following surgery, showed no recurrence of the ABC lesion (Fig. 4).

Patient 6 developed signs of avascular necrosis of the capital femoral epiphysis 12 weeks post-procedure. Nevertheless, the cyst had completely healed.

Patient 7 had a good response to her doxycycline treatment with reduction in the cystic lesion (Fig. 5) but was found to have a closed proximal femoral physis and subsequently developed trochanteric overgrowth that led to a leg length discrepancy. A pathological fracture just prior to the injection contributed to varus angulation and shortening but it is not possible to exclude a contribution from the injection itself. She underwent contralateral left distal femoral epiphysiodesis to equalize leg length discrepancy.

Discussion

Surgical treatment of ABCs has many challenges, including: hemorrhage, damage to other structures, and high recurrence rates [13]. Percutaneous doxycycline for the treatment of ABCs has been documented since 2013 [12] but there is limited published experience with the technique. This case series shows a single dose of percutaneous doxycycline to be effective in treating ABC. Clinical observation shows that it may take months for the lesion to resolve completely. It cannot be said if a second dose hastened resolution of the lesions in this series.

This contrasts with a previous study [12] where patients received a mean of five doses of percutaneous doxycycline (range, 2–14). Patients in that study had follow-up imaging at 6 weeks after the first treatment and 10 weeks after subsequent treatments. Subsequent treatments were scheduled 8 weeks after the first treatment and at 12-week intervals thereafter. Indication for further treatment included incomplete healing of lytic areas or if the area was not stable after two treatments. Patients were observed for 5 years for recurrence- defined as new areas of bony lysis or lucent expansion. A recent study suggested treatment with doxycycline in a calcium phosphate cement to provide structural support and reduce the need for repeat injections [22].

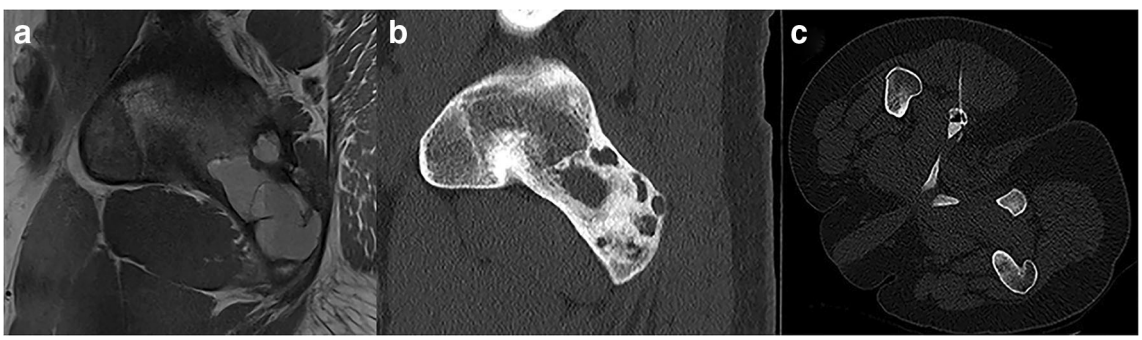

Fig. 3 Patient 5. Image of 15-year-old male with an ABC of the pelvis. **a** Sagittal MRI pre-procedure; **b** sagittal CT 14 months post-procedure; note shrinkage of cavities and new bone formation around them with cortical thickening, **c** Axial CT peri-procedure showing needle in lesion

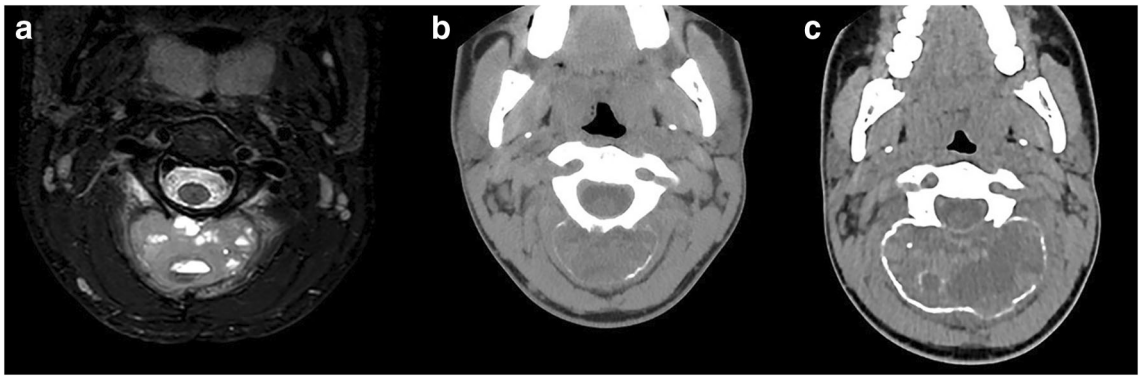

Fig. 4 Patient 4. Axial plane imaging of an 18-year-old male with an ABC of the cervical spine. **a** MR pre-procedure; **b** CT pre-procedure; **c** CT 2 months post-procedure showing early bone formation within lesion but increasing size and extension into laminae prompting surgical resection

In six of seven patients in this series, there was clear clinical and imaging evidence of healing response after one injection. Although three patients went on to receive a second injection, the indications for doing so were not compelling. It is the authors' contention that ideal management would be to do a single injection and observe for a period of at least 12 weeks before contemplating further injection, since the healing response, in our experience, can take some time to manifest. Avoiding more than one injection is desirable in order to decrease both radiation exposure and anesthetic time, especially in the pediatric population.

This series included two patients with proximal femoral juxtaphyseal lesions, both of whom already had pathological fractures at the time of treatment. One required corrective surgery due to growth arrest of her cartilage plate (Fig. 5) and the other developed femoral head osteonecrosis. It is possible that these complications were secondary to the ABC and fracture, rather than the doxycycline injection, but it impossible to be certain. In another study, the epiphyseal plate was involved in nine of 39 juxtaphyseal ABC lesions, with growth disturbance occurring in five (56%) after surgical treatment [23]. It was also reported that two patients had growth disturbances despite no evidence of epiphyseal plate involvement [23]. In a series of 16 patients with juxtaphyseal ABC treated with doxycycline treatment, seven patients had physeal involvement (five in the humerus, one in the tibia and one in the femur) [24]. Five of these (71%) had focal growth arrest but only one had a slight growth deformity that did not require corrective treatment.

This series includes one patient who had spontaneous resolution of her ABC after two needle biopsies and an open biopsy. Various authors have noted spontaneous resolution of ABC after a biopsy [25, 26]. This prompted one group to develop a biopsy technique that combined limited percutaneous curettage of the lining membrane of various quadrants of the cyst, with the intention to cure [15]. In a series of 102 patients, 81% were successfully treated without recurrence [15]. Another series of 17 compared percutaneous curettage versus standard intralesional excision and found success rates were 78 and 87%, respectively [27].

This study also includes one patient who went on to have surgery due to expansion of the lesion on imaging. This could represent the expansion in response to a mechanical disturbance to the lesion as described by previous authors [25, 26, 28]. It is important to note that this patient's procedure was difficult due to patient discomfort on IV sedation, whereas all

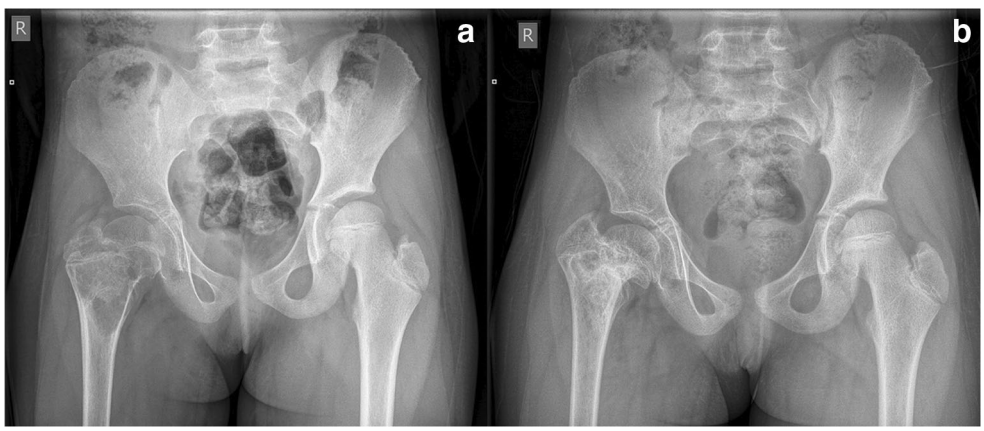

Fig. 5 Patient 7. AP radiograph of 9-year-old female with an ABC of the proximal femur. **a** Pre-procedure; **b** at 5 months post-procedure showing healing of the lesion but premature growth plate closure

other patients had the procedure done under GA. The excision specimen did show a positive histological response to doxycycline, suggesting that healing was commencing.

Four radiologic phases of ABC development have been proposed, (1) the initial phase: osteolysis of bone margins and periosteal reaction; (2) the growth phase: bony destruction with poor demarcation and the absence of bony shell and septa at times; (3) the stabilization phase: classic appearance with expansion and distinct bony shell and osseous septa; and (4) the healing phase: transition into a bony mass [29]. Several authors have reported an increase in size immediately after a biopsy (up to 5 months) with a secondary reduction in size [25, 26, 28].

Limitations

The single cohort study is limited by the small number of patients and its retrospective analysis. The follow-up period (14–60 months) may not encapsulate all recurrences of the lesions. Histological diagnosis was not done in all patients. This was a single arm study with no matched controls and the effectiveness of doxycycline treatment cannot be compared with other treatment modalities. Other injection regimes (including biopsy without pharmaceutical) have been reported as effective and it is not possible to separate the effect of doxycycline from that of needle placement in the ABC in this series. Other confounding factors include the presence of pathological fractures. Although a randomized prospective trial would be ideal for evaluating doxycycline injection for ABC, its sporadic occurrence and the heterogeneity of the patient population makes this difficult in practice for most centers.

Conclusions

Percutaneous doxycycline should be considered a viable primary treatment option for ABC. The optimum number and timing of injections has yet to be determined but, in this series, a single injection produced signs of healing in six of seven patients, histological response in the seventh, and was the only required treatment in three. The authors' contention is that it is reasonable to treat with a single injection and to withhold further treatment unless there is no sign of healing after a period of approximately 12 weeks.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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