Aus der Klinik für Orthopädie, Physikalische Medizin und Rehabilitation

Klinik der Ludwig-Maximilians-Universität München

Direktor: Prof. Dr. Dipl.-Ing. Volkmar Jansson

Aneurysmale Knochenzysten:

Klinik, Therapie und Ergebnisse

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

vorgelegt von

Ferdinand Grahneis

aus München

2021

Mit Genehmigung der Medizinischen Fakultät

der Universität München

Berichterstatter:	Prof. Dr. med. Hans Roland Dürr
Mitberichterstatter:	Prof. Dr. med. Christian Kammerlander PD Dr. med. Jochen Hubertus
Dekan:	Prof. Dr. med. dent. Reinhard Hickel
Tag der mündlichen Prüfung:	06.05.2021

Einleitende Zusammenfassung der schriftlichen, kumulativen Promotion

gemäß § 4a der Promotionsordnung der LMU vom 1. Juni 1983

in der 11. Fassung vom 15. September 2016

Eidesstattliche Versicherung

Ich, Ferdinand Grahneis, versichere hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Thema „*Aneurysmale Knochenzysten: Klinik, Therapie und Ergebnisse*“ selbstständig angefertigt habe, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

I hereby confirm that the dissertation „*Aneurysmale Knochenzysten: Klinik, Therapie und Ergebnisse*” is the result of my own work and that I have only used sources or materials listed and specified in the dissertation.

10.05.2021	Ferdinand Grahneis
---	---
München, den / Munich, date	Unterschrift / signature
	Ferdinand Grahneis

Inhaltsverzeichnis

1 Abkürzungsverzeichnis

ABC	Aneurysmal bone cyst, aneurysmale Knochenzyste
CT	Computed tomography, Computertomographie
GCT	Giant cell tumour, Riesenzelltumor
IU/ IE	International Units/ Internationale Einheiten
mg	Milligramms, Milligramm
MMP	Matrix-Metalloproteinase
MRI/ MRT	Magnetic resonance imaging/ Magnetresonanztomographie
RANK	Cytokine receptor activator of nuclear factor-kappa B
RANKL	Cytokine receptor activator of nuclear factor- kappa B ligand
USP6	Ubiquitin carboxyl-terminal hydrolase 6
VEGF	Vascular endothelial growth factor

2 Publikationsliste

2.1 Veröffentlichung I

Grahneis F, Klein A, Baur-Melnyk A, et al. Aneurysmal bone cyst: A review of 65 patients. J Bone Oncol. 2019;18:100255. Published 2019 Aug 6. doi:10.1016/j.jbo.2019.100255 (IF 2.87)

2.2 Veröffentlichung II

Dürr HR, Grahneis F, Baur-Melnyk A, et al. Aneurysmal bone cyst: results of an off label treatment with Denosumab. BMC Musculoskelet Disord. 2019;20(1):456. Published 2019 Oct 20. doi:10.1186/s12891-019-2855-y (IF 2.0)

3 Einleitung und Grundlagen

Trotz des benignen Charakters sind primäre Aneurysmale Knochenzysten (Aneurysmal Bone Cyst, im Weiteren als ABC bezeichnet) oft aggressive und schwer zu therapierende Läsionen, die zu lokalen Rezidiven neigen. Sie kommen typischerweise in den Metaphysen der langen Röhrenknochen oder in der Wirbelsäule vor, und wurden von Jaffe und Lichtenstein in 1942 erstmalig beschrieben [1-3].

ABC treten am häufigsten bei Kindern und jungen Erwachsenen auf. Mit einer Inzidenz von 1.4/100,000 stellen sie etwa 1% aller gutartigen Knochentumore dar [16]. Die Geschlechtsverteilung ist ausgeglichen. Die Läsionen sind exzentrische Osteolysen des epi-/metaphysären Knochens mit klarer Abgrenzung. Sie wachsen expansiv und zeigen bei Krankheitsprogression eine Auftreibung des Knochens, mit Ausdünnung der Kortikalis (sogenanntes „blow out"-Phänomen). Histologisch zeigen sie sich blutgefüllt und durch fibröse Septen getrennt. Sie weisen Fibroblasten, osteoclastenartige Riesenzellen und reaktiven Geflechtknochen auf [4]. Weichteilmanifestationen sind selten, wurden aber seit 1972 in einigen Fällen beschrieben [5].

Lange wurde davon ausgegangen, dass ABC ausschließlich reaktiv durch Gefäß-Malformationen entstehen, durch welche der venöse Druck gesteigert wird, und es zur Dilatation des intraossären Gefäßnetzwerkes kommt [6, 7]. 1999 demonstrierten Panoutsakopoulos et al. jedoch, dass bei primären ABC eine balancierte chromosomale Translokation (t[16;17] [q22;p13]) vorliegt[8], die das Hydrolase 6 (USP6)-Gen, welches auf dem Chromosom 17p13 liegt, involviert. Somit wurde die neoplastische Genese der ABC erwiesen. Die USP6-Translokation kann in ca. 75% der Fälle aufgefunden werden[9]. In ausgewählten Fällen kann dies eine Option zur Differenzierung von primären ABC und sekundären Läsionen oder anderen Tumoren wie dem teleangiektatischen Osteosarkom sein. Diese Translokation führt zur vermehrten Produktion von TRE17, einer Protease, die die Aktivität der Matrix-Metalloproteinase (MMP)-9 und MMP-10 steigert [10]. Diese wiederum ist, über einen autokrinen Mechanismus mit knochenmorphologischer Dysregulation und verstärkter Ausschüttung von VEGF (Vascular Endothelial Growth Factor), mit der Blockierung der Osteoblastenreifung assoziiert. Durch diesen Mechanismus wird die Vaskularisation verstärkt [11].

Die Behandlung der ABC hat sich über die Jahre verändert. Eine weite Resektion der Läsion ist in den meisten Fällen aufgrund erheblicher funktioneller Einschränkung keine Option, weshalb intraläsionale Eingriffe, wie die Kürettage, die Standardbehandlung darstellen[12]. Aufgrund hoher Rezidivraten von bis zu 50% wurden zahlreiche adjuvante Behandlungsmethoden verwendet. Die gängigsten sind heute Knochenzementfüllung, Argon-Laser, Phenol, Ethanol und Cryotherapie [12]. Weniger invasive Therapieformen, wie aggressive Biopsie („Curopsie") [13], selektive arterielle Embolisation [14, 15], Sklerosierung mit Ethibloc oder Polidocanol [16], und die systemischer Therapie mit RANKL-Inhibitoren (Denosumab) [17], wurden erprobt.

Denosumab ist ein humaner monoklonaler Antikörper, der spezifisch an ein Protein, das Receptor Activator of Nuclear factor-Kappa B Ligand (RANKL) genannt wird, bindet [18]. In der Folge wird verhindert, dass RANKL den RANK-Rezeptor der Osteoclasten aktiviert. Dadurch wird die Osteoclastenfunktion inhibiert. Denosumab zeigte bei irresektablen Riesenzelltumoren des Knochens ein gutes Ansprechen, weshalb man prinzipiell auf ähnliche Resultate bei der Behandlung der ABC hoffen kann, da eine Ähnlichkeit beider Läsionen besteht [19]. Es existiert noch kein etabliertes Protokoll oder eine Behandlungsempfehlung für Denosumab bei ABC. Zum Zeitpunkt der Veröffentlichung unserer Studie gab es zur Behandlung der ABC mit Denosumab nur zwei Fallstudien mit jeweils 9 Patienten [17, 20, 21] sowie 11 weiteren Fällen, die als individuelle Fallberichte publiziert wurden [21-30].

4 Zielsetzung der Untersuchungen

Das Ziel dieser Arbeit ist die Aufarbeitung von Klinik, Radiologie und den Ergebnissen der diversen Therapieoptionen der ABC. In der Publikation „Aneurysmal bone cyst: A review of 65 patients" werden alle in unserer Klinik behandelten Patienten vorgestellt, welche hauptsächlich mit Kürettage, mit und ohne adjuvante Phenolisation, und auch mit weniger invasiven Interventionen behandelt wurden. In der zweiten Studie „Aneurysmal bone cyst: results of an off label treatment with Denosumab" wird eine Serie von sechs Patienten vorgestellt, die off-label mit Denosumab behandelt wurden.

Die geringe Fallzahl dieser Läsion und die Bandbreite an Behandlungsoptionen macht es nötig, dass viele Fälle beschrieben und publiziert, und darüber hinaus zentrumsübergreifend verglichen werden. Wir hoffen, dass wir mit der Veröffentlichung unserer Erfahrungen dazu beitragen können, diese Läsion besser zu verstehen und die Therapiekonzepte dieser Erkrankung zu optimieren.

5 Zusammenfassung

5.1 Methode

Zwischen 1982 und 2014 wurden in unserer Klinik 65 Patienten mit histologisch bestätigter ABC behandelt. Davon waren 61 intraossär und 4 im Weichgewebe lokalisiert. Die Datensätze und vorhandene Bildgebung aller Patienten wurden retrospektiv erfasst und analysiert. Nach Zustimmung der Ethikkommission der Fakultät (18-373) wurden alle Patienten persönlich kontaktiert, entweder in unserer Ambulanz oder im Rahmen einer telefonischen Befragung. Eine schriftliche Einverständniserklärung, aller in dieser Studie inkludierten Patienten, wurde eingeholt.

Bei der Behandlung gab es ein weites Spektrum an Therapieoptionen. Die meisten Patienten wurden chirurgisch behandelt, mit und ohne Adjuvans. Außerdem wurden minimalinvasive

Polidocanolinjektionen, interventionelle arterielle Embolisationen und, seit 2011, auch nicht-invasive Therapie mit RANKL-Inhibitoren eingesetzt. In diesen 6 Fällen wurde Denosumab off-label, im bei GCT etablierten Behandlungsregime, eingesetzt [31]. Indikation für letzteres war die erwartete unverhältnismäßige Morbidität bei chirurgischer Intervention, bei primären Läsionen oder bei Rezidiven, oder als adjuvante Rezidivprophylaxe nach chirurgischer Intervention. Denosumab wurde subkutan in einer Dosis von 120 mg an Tag 1, 8, 15, 29 und danach alle 4 Wochen appliziert. Eine Dosisreduktion erfolgte bei einem 6 Jahre alten Jungen und bei manchen Patienten gegen Ende der Therapie. Um eine Hypokalzämie als Nebenwirkung zu vermeiden, wurden täglich Vitamin D 1000 IU und Calcium 500 mg supplementiert. Kontrolluntersuchungen wie MRT, Röntgen oder in spezifischen Fällen eine CT-Bildgebung wurden alle 3 Monate im ersten Jahr, und alle 6 Monate im zweiten Jahr der Therapie durchgeführt. Weitere Kontrolluntersuchungen erfolgten nach individueller Entscheidung. Wie in der Literatur beschrieben, sollten ABC jedoch erst als geheilt betrachtet werden, wenn 2 Jahre nach Ende der Therapie kein Rezidiv aufgetreten ist [14]. Die Therapieoptionen wurden bei entsprechender Indikation kombiniert, sodass zusammengefasst 80 Interventionen an 65 Patienten durchgeführt wurden.

Zur Datenanalyse wurde die MedCalc®-Software benutzt. Zur statistischen Analyse wurde das Rezidiv-freie Überleben mithilfe des Kaplan-Meier-Verfahrens berechnet. Die Signifikanzanalyse wurde mittels Log-Rank-Test, beziehungsweise Chi-Quadrat-Test, durchgeführt.

5.2 Ergebnisse

Die meisten unserer Patienten waren zum Zeitpunkt der Behandlung in ihrer zweiten Lebensdekade. Im Durchschnitt waren sie 25,3 ± 16,0 Jahre alt. Das Alter der Patienten reichte von 4 bis 74. Das Verhältnis männlicher zu weiblichen Patienten war 0,94. 61 der ABC waren intraossär und 4 im Weichgewebe lokalisiert. Von den intraossären Läsionen befanden sich 23% im Becken, 18% im Femur, 16% in der Tibia, 10% in der Wirbelsäule, 8% im Humerus, je 5% in Hand und Fuß, je 3% in Radius und Ulna, und je eine in Rippen, Patella und Fibula.

Zur Diagnosestellung führten am häufigsten die Symptome Schmerz (89%) und lokale Schwellung (15%). Die maximale Ausdehnung der Läsionen wurde in der Schnittbildgebung ermittelt. Sie reichte von 1 bis 30 cm und ergab im Durchschnitt 5,2 cm ± 4,0 cm.

Sechs Läsionen wurden reseziert (4 im Weichgewebe und 2 im Knochen). Hier kam es in keinem Fall zum Rezidiv. 5 Patienten wurden interventionell mit Polidocanolinjektionen (3) oder Embolisation und Denosumab behandelt (2). Bei Therapie mit Embolisation und Denosumab zeigte sich in beiden Fällen eine Stabilisation der Läsion, ohne weiteren Behandlungsbedarf. Die Anwendung von Polidocanolinjektionen führten auch zur Stabilisation der Läsion eines Patienten. Bei den zwei anderen Patienten musste anschließend noch eine Kürettage mit adjuvanter Phenolisation durchgeführt werden,

um zum selben Ergebnis zu kommen. Von diesen beiden wiederrum zeigte sich bei einem eine stabile Persistenz, beim anderen Patienten musste eine zweite Kürettage durchgeführt werden, diesmal ergänzt durch Phenol und Denosumab, was auch zu einer stabilen Persistenz führte.

Von 54 primären Kürettagen wurden 33 ohne adjuvante Phenolisation durchgeführt. In dieser Gruppe wurden 21 Läsionen geheilt (64%), 3 (9%) zeigten eine stabile Persistenz und 9 (27%) hatten ein Rezidiv. Von diesen 9 Rezidiven wurden 7 erneut kürettiert, was bei 6 zur Heilung führte und in einem Fall zur Persistenz, auch nach dritter Kürettage und Denosumabtherapie. Ein Rezidiv wurde durch Polidocanolinjektion geheilt und ein Patient entschied sich gegen eine weitere Therapie.

Von den 21 primären Kürettagen mit adjuvanter Phenolisation führten 16 (76%) zur Heilung, 3 (14%) zeigten eine stabile Persistenz (eine davon unter adjuvanter Denosumabtherapie), bei 2 Patienten kam es zu einem Rezidiv. Bei einem dieser Patienten wurde eine zweite Kürettage mit Phenol durchgeführt, was zur Heilung führte. Der andere Patient stellte sich zur weiteren Behandlung in einer anderen Klinik vor. Das Endergebnis ist uns nicht bekannt.

Zusammengenommen wurden 80 Interventionen bei 65 Patienten durchgeführt. Von den 66 Kürettagen führten wir 39 ohne und 27 mit adjuvanter Phenolisation durch. Heilung wurde in 25 (64%) bzw. 19 (70%) der Fälle erreicht. Zu Persistenzen kam es in jeweils 5 (12%/19%), zu Rezidiven in 9 (23%) bzw. 3 (11%) Fällen. Der Gesamtmittelwert des Follow-ups lag bei 119 Monaten (Median 82 Monate; 3,1 bis 408 Monate). Bei 15 Patienten (19%) kam es zu Lokalrezidiven (in den meisten Fällen (80%) innerhalb der ersten 2 Jahre nach erstmaliger Therapie, bei einem Patienten jedoch auch noch über 8 Jahre nach der initialen Intervention). Bei Rezidivläsionen war das Risiko eines weiteren Rezidivs erhöht. Dieser Unterschied erreichte in unserer Studie jedoch keine statistische Relevanz.

Die Denosumabbehandlung, der hierfür ausgewählten Patienten, erfolgte zwischen 2011 und 2018. Es waren 6 Patienten (4 weiblich und 2 männlich) im Durchschnittsalter von 17 Jahren (6 bis 30 Jahren). Das führende Symptom war bei allen Patienten Schmerz, mit einer mittleren Dauer von 14 Monaten (1-42 Monate) vor Diagnosestellung. Zwei der Läsionen waren im Steißbein lokalisiert, und jeweils eine in Becken, Talus, im distalen Femur und distalen Radius. Bei beiden Patienten mit sakraler ABC wurde vor der initialen Behandlung eine Feinnadelbiopsie durchgeführt. Bei 4 der Kinder und Jugendlichen kam es nach Absetzen des Denosumabs zu einer schweren Hyperkalzämie als Reboundphänomen.

5.3 Schlussfolgerungen

Die Kürettage bleibt die Standardtherapie der ABC. Die Anwendung einer adjuvanten Phenolisation konnte keinen signifikanten Einfluss auf die Rezidivraten zeigen. Die Resektion der ABC führt zu einer Rezidivrate von 0%, ist aber nur in sehr wenigen Fällen durchführbar. Minimalinvasive Verfahren können zur Heilung oder zu tolerabler Persistenz führen, sie müssen jedoch mehrmals durchgeführt

werden und konnten bisher, im Vergleich mehrerer Kliniken, noch keine eindeutigen Ergebnisse hervorbringen.

Denosumab ist ein weiteres, nicht invasives Mittel zur Behandlung von ABC. Der Einsatz ist vor allem in chirurgisch kritischen Lokalisationen, wie dem Becken und der Wirbelsäule, interessant. Außerdem könnte der adjuvante Einsatz nach intraläsionaler Kürettage zur Reduktion von Lokalrezidiven bei aggressiven Läsionen führen. Die häufigste der schweren Nebenwirkungen von Denosumab, die aseptische Kiefernekrose, wurde bei der Behandlung der ABC bis jetzt noch nicht beschrieben. Jedoch bleibt, aufgrund des niedrigen Alters einiger Patienten, die schwere, reaktive Hyperkalzämie auch Monate nach Therapieende ein beträchtliches Risiko. Deswegen sollten regelmäßige Kontrollen der Laborparameter für mindestens zwei Jahre nach Ende der Therapie durchgeführt werden. Allen behandelnden Ärzten muss bewusst sein, dass die Indikation von Denosumab bei ABC off-label geschieht und daher einer intensiven, interdisziplinären Diskussion mit dem Patienten oder seiner Familie bedarf.

6 Summary

6.1 Methods

In our Institution 65 patients with primary ABC were treated between 1982 and 2014. All of these were histologically proven. After attaining approval of our institution's ethics committee (#18-373), clinical data and imaging studies were collected from patients medical records and systematically reviewed. All patients were contacted personally, either in our outpatient clinic or in a telephone survey. Written consent of all patients included in this study was acquired.

A wide range of treatments was provided. Most patients were treated surgically, with and without adjuvants. In selected cases arterial embolizations or minimal invasive Polidocanol injections were performed. Since 2011 we also provided non-invasive therapy with RANKL-Inhibitors to treat patients with ABC. Indication had been either recurrence prevention in an adjuvant setting after surgery, or expected unreasonable morbidity of surgical treatment. In these 6 cases, Denosumab was used off-label, in the protocol established for giant cell tumor (GTC) of bone [31]. Treatment was administered on days 1, 8, 15, 29 and every 4 weeks afterwards, in a dose of 120 mg subcutaneously. Dose reduction was possible in a 6-year-old boy and in some patients towards the end of their treatment. To avoid hypocalcemia as a side effect, Vitamin D 1000 IU and Calcium 500 mg were supplemented daily. Follow-up imaging such as radiographs, magnetic resonance imaging (MRI) or, in selected cases, computed tomography (CT) were performed routinely 4 times in the first year, and 2 times in the second year of therapy. Further investigations were based on individual decision. Since recurrence has been described at later points after the treatment, ABC can be considered healed if there is no recurrence for

2 years after cessation of treatment [14]. A combination of the treatments listed was provided in some cases, so that in total, 80 procedures were performed on 65 patients.

For data analysis software, MedCalc® software was used. Statistical analysis was performed according to the Kaplan-Meier method to calculate the recurrence-free survival. Log-Rank test or Chi-Square test were used for significance analysis.

6.2 Results

At the time of treatment, most of our patients were in their second decade of life, with a mean age of 25,3 ± 16,0 years, ranging from 4 to 74 years. The ratio of male to female patients was 0.94. In 61 cases, the tumors were located in bone, and in 4 cases we saw manifestation in soft tissue. Of the skeletal lesions, 23% were located in the pelvis, 18% in the femur, 16% in the tibia, 10% in the spine, 8% in the humerus, 5% each in hand and foot, 3% each in radius and ulna and one each in ribs, patella and fibula.

The most common symptoms leading to the diagnosis were pain (89%) and local swelling (15%). The maximum extent of the lesions was determined by cross-sectional imaging. It ranged from 1 to 30 cm with a mean maximum diameter of 5.2 cm ± 4.0 cm.

In six cases, resection was achieved (2 bone and 4 soft tissue). None of these lesions showed recurrence. 5 patients were treated with interventional procedures. 2 of them with embolization and Denosumab, which resulted in stable persistent disease without the need for further treatment. 3 patients were treated with polidocanol injections, which led to the same result in one patient. In the other two patients, curettage with adjuvant phenolization had to be performed. Of these two patients, one showed stable persistent disease and the other had to receive second curettage, this time complemented by phenol and Denosumab, finally leading to stable persistent disease.

Out of 54 primary curettages, 33 were performed without adjuvant penalization. This led to cure in 21 (64%) cases, 3 (9%) resulted in stable persistent disease and 9 (27%) showed recurrence. Of these 9 recurrent lesions, 7 underwent a second curettage, healing 6 and causing persistent disease in one case, even after a third curettage and Denosumab treatment. One recurrence was cured by polidocanol injection and one patient decided against further treatment.

Out of 21 primary curettages with adjuvant phenolization, 16 lesions were cured (76%), 3 (14%) showed stable persistent disease (one of them with adjuvant Denosumab therapy), 2 patients showed local recurrence. In one of these patients a second curettage with phenol was performed, which led to healing. The other patient chose another institution for further treatment. The final outcome is not known to us.

In total, 80 interventions were performed on 65 patients. Of the 66 curettages, 39 were performed without and 27 with adjuvant phenolization. The lesions were cured in 25 (64%) and in 19 (70%) cases, showed persistent disease in 5 cases each (12%/19%) and recurrence in 9 (23%) and 3 (11%) cases,

respectively. The total mean follow-up was 119 months, ranging from 3.1 to 408 months, with a median of 82 months. In 15 patients (19%), local recurrence was seen. Most of these (80%) occurred within the first 2 years after the initial intervention. But in one case recurrence became evident more than 8 years after the initial treatment. In recurrent lesions, the risk of further recurrence was increased, without reaching significance in our series.

The Denosumab treatment of 6 selected patients was carried out between 2011 and 2018. 4 female and 2 male patients with an average age of 17 years (ranging from 6 to 30 years) were treated for histologically proven ABC. The leading symptom in all patients was pain, with a mean duration of 14 months (1 to 42 months) before diagnosis. Two lesions were located in the sacrum, and one each in pelvis, talus, distal femur and distal radius. In both patients with sacral ABC a fine needle biopsy was performed before the initial treatment. In 4 of the children and adolescents severe hypercalcemia occurred as a rebound phenomenon after discontinuation of Denosumab.

6.3 Conclusion

Curettage remains the standard treatment of ABC. The use of adjuvant phenolization could not show significant influence on recurrence rates. While resection of the lesion showed no recurrence at all, it is feasible only in very few localizations, predominantly in soft tissue. Minimally invasive procedures have been able to cure ABC or lead to tolerable persistence of the residual cysts. However, these procedures have to be performed several times and have not yet been able to produce homogenous results in comparison of data from several institutions.

Denosumab adds a non-invasive treatment to the arsenal against ABC. The application is particularly interesting in surgically critical locations, such as the pelvis and the spine. As adjuvant treatment after surgical intervention, it may reduce the recurrence rate in aggressive lesions. The most common of the severe complications of Denosumab, osteonecrosis of the jaw, has not been described in patients treated for ABC. But due to the low age of some patients, severe reactive hypercalcemia remains a significant risk even months after the end of therapy. Therefore, regular checks of laboratory parameters should be performed for at least two years after the end of therapy. Since the indication of Denosumab for ABC is off-label, there should be an elaborate discussion with the patient or their family, before the beginning of each treatment.

7 Veröffentlichung I

Journal of Bone Oncology 18 (2019) 100255

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Aneurysmal bone cyst: A review of 65 patients

Ferdinand Grahneis[a], Alexander Klein[a], Andrea Baur-Melnyk[b], Thomas Knösel[c], Christof Birkenmaier[a], Volkmar Jansson[a], Hans Roland Dürr[a,*]

[a] Musculoskeletal Oncology, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Marchioninistr. 15, D-81377 Munich, Germany
[b] Department of Radiology, University Hospital, LMU Munich, Germany
[c] Institute of Pathology, University Hospital, LMU Munich, Germany

ARTICLE INFO

Keywords:
Aneurysmal bone cyst
Curettage
Recurrence
Phenol

ABSTRACT

Background: Aneurysmal bone cysts (ABC) are benign but locally aggressive lesions. The treatment of ABC has evolved over the years, but curettage with or without local adjuvants still represents the standard. Less invasive methods such as embolization, sclerotherapy or RANKL inhibitors (Denosumab) are also established. The aim of this study was to report and compare the results of a series of patients mainly treated with curettage with and without subsequent phenolization.

Methods: 65 patients with the unequivocal diagnosis of primary ABC were treated. 61 of them were located within the bone whereas 4 patients had an ABC of the soft tissues. All patient were treated surgically by means of curettage with or without adjuvants, resection, or with minimally invasive methods such as Polidocanol injections, embolizations or Denosumab treatment. In total 80 procedures had been performed.

Results: Our patients had a mean age of 25.3 ± 16.0 years, ranging from 4 to 74 years. The most common skeletal locations were the pelvis in 23%, the femur in 18%, the tibia in 16% and the spine in 10%. Six lesions were resected and showed no recurrence. 5 patients were treated with polidocanol injections ($n = 3$) or embolization plus systemic treatment with Denosumab ($n = 2$). With embolization and Denosumab both patients showed stable disease and required no further treatment. Polidocanol injections resulted in stable disease with no further treatment required in one patient and in subsequent curettage with adjuvant phenolization in two other patients.

In 54 initial curettages 21 were performed with adjuvant phenolization. In this group, 16 lesions healed (76%), 3 showed persistent disease and 2 patients had a local recurrence (9%). Out of 33 patients without phenolization 21 (64%) healed, 3 showed stable persistent disease and 9 (27%) experienced a recurrence. In total we performed 66 curettages, 27 with and 39 without adjuvant phenol treatment. Resolution was achieved in 19 (70%) and 25 (64%) of cases. respectively. Persistent disease was evident in 5 cases each and recurrence in 3 and 9 cases, respectively (n.s.).

Conclusion: Curettage is still the standard of treatment for ABC. Local recurrence does not depend on the use of adjuvant phenol as shown in this and other studies. Minimally invasive methods such as selective embolization and injections of sclerosing agents may result in healing or at least in tolerable persistence of residual lesions but needs repetitive treatments and does not show homogenous results throughout the institutions. Denosumab appears to be an additional option, especially in surgically critical locations such as the spine or the sacrum.

1. Introduction

Aneurysmal bone cyst (ABC) are benign intraosseous or rarely soft tissue lesions and were first described by Jaffe and Liechtenstein in 1942 [1]. ABC's are considered benign yet locally aggressive lesions with a potential for local recurrence, and they typically appear in the metaphysis of the long bones and in the vertebral column [2,3]. ABC's are most often seen in children and young adults with no sex predilection. These lesions are lytic, usually eccentrically located and expansive with well-defined margins. There are blood-filled, separated by fibrous septa, with fibroblasts, osteoclast-type giant cells and reactive woven bone [4]. Soft tissue lesions are rare but since 1972 have been described in a number of cases [5].

Aneurysmal bone cysts were originally thought to be reactive in

* Corresponding author.
E-mail address: hans_roland.duerr@med.uni-muenchen.de (H.R. Dürr).

https://doi.org/10.1016/j.jbo.2019.100255
Received 19 March 2019; Received in revised form 2 August 2019; Accepted 4 August 2019
Available online 06 August 2019

nature, caused by a circulatory abnormality leading to an increased venous pressure and resulting in dilation of the vascular network [6,7]. Nowadays, the neoplastic nature of aneurysmal bone cyst has been proven since in 1999, Panoutsakopoulos et al. demonstrated a balanced chromosomal translocation t(16;17)(q22;p13) as a cytogenetic abnormality in primary aneurysmal bone cyst [8] involving the USP6 gene, located on chromosome 17p13. After establishing this USP6 translocation as a diagnostic tool, it has been found in approximately 75% of the cases [9]. Thus differentiating primary ABC`s from secondary lesions or other tumors such as teleangiectatic osteosarcoma had become much more easier.

The treatment concepts of ABC have evolved over the years. Resection is not an option in most of the cases leaving intralesional procedures such as curettage as standard of care [10]. Due to local recurrence rates of more than 50%, various adjuvant treatments have been used. Most common are PMMA bone cement, argon beam, phenol, ethanol and cryotherapy [10]. Less invasive methods such as aggressive biopsy ("Curopsy") [11], selective arterial embolization [12,13], sclerotherapy with ethibloc or polidocanol [14] and systemic therapy with RANKL inhibitors (Denosumab) [15] have been tried. The aim of this study was to report and compare the results of a series of patients mainly treated by curettage with and without adjuvant phenol treatment and also by less invasive interventions.

2. Material and methods

Between 1982 and 2014, 65 patients with histologically proven primary ABC were treated at our institution. 61 of these ABC were located in bone whereas 4 patients had an ABC of the soft tissues. The medical records and imaging studies of all cases were reviewed after obtaining institutional review board approval and each patient was either contacted by means of a telephone survey or seen in the outpatient clinic. All patient had been treated surgically by curettage with or without adjuvants, resections, or with minimally invasive methods as Polidocanol injections, embolizations or Denosumab therapy. In total, 80 procedures were performed.

2.1. Statistical analysis

For statistical analysis, the recurrence-free survival was calculated according to the Kaplan-Meier method. Significance analysis was performed using the Log-Rank test or the Chi-Square test, respectively. The data analysis software used was MedCalc®.

3. Results

Our patients had a mean age of 25.3 ± 16.0 years at the time of treatment, ranging from 4 to 74 years, most of them were in their second decade of age (Fig. 1). The male to female ratio was 0.94. The most common skeletal locations were the pelvis in 23%, the femur in 18%, the tibia in 16% and the spine in 10% followed by the humerus in 8%, the hand and the foot in 5% each, radius and ulna in 3% each and patella, ribs and fibula in one case each.

The main symptoms that had led to the diagnosis were pain in 89% and local swelling in 15%. As measured on cross-sectional imaging, the mean maximum diameter of the lesions was 5.2 cm ± 4.0 cm, ranging from 1 to 30 cm.

The therapy and outcomes are shown in Fig. 2. Six lesions were resected (4 soft tissue and 2 bone) and showed no recurrence. 5 patients were treated with polidocanol injections ($n = 3$) or embolization and Denosumab ($n = 2$). With embolization and Denosumab both patients showed stable disease and need no further treatment. Polidocanol injections caused stable disease with no further treatment in one patient and curettage with adjuvant phenolization led to the same result in two additional patients. Of those, one patient showed stable persistent disease after the procedure, the second needed a second curettage

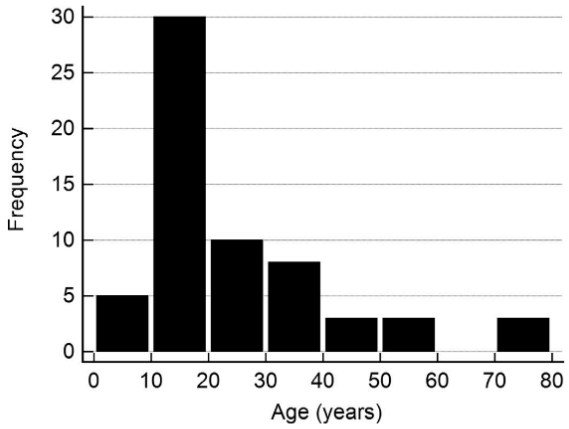

Fig. 1. Age distribution in 65 patients with aneurysmal bone cysts.

including now also phenol and Denosumab which lead to stable persistent disease.

Out of 54 primary curettages, 21 were performed with adjuvant phenolization. In this group, 16 lesions healed (76%), 3 showed persistent disease (one with adjuvant Denosumab therapy) and 2 patients had a local recurrence. One of those 2 recurrences had a second curettage with phenol and subsequently healed, the other opted for treatment at another institution with the final outcome unknown.

Out of 33 primary curretages without adjuvant phenolization, 21 (64%) healed, 3 showed stable persistent disease and 9 (27%) had a recurrence. Out of those 9 recurrent cases, 7 had a second curettage which resulted in healing in 6 patients and in persistent disease even after a third curettage and Denosumab treatment in one patient. One recurrence healed after a polidocanol injection and one patient opted for no further therapy.

In total, we performed 66 curettages, 27 with and 39 without adjuvant phenolization. Healing was achieved in 19 (70%) and in 25 (64%) cases, respectively. Persistent disease was evident in 5 cases each and recurrence in 3 and 9 cases, respectively (Fig. 3, n.s.). Overall, 80 interventions were performed on 65 patients.

The total mean follow-up was 119 months (median 82 months, range 3.1–408 months). Local recurrence was seen in 15 (19%) patients and with most of them (80%) during the first 2 years after initial treatment, but one patient as late as more than 8 years after the intervention (Fig. 4). In cases where the lesion had already been a recurrent disease, the risk of further recurrence was increased, but this difference did not reach significance in our series (Fig. 5). A comparison of this data to the published series is listed in Table 1.

4. Discussion

ABC is a benign but locally aggressive lesion with no unequivocally defined primary treatment option. En bloc resection is not an option for the majority of patients because of the resulting disability/the required reconstructive surgery on the background of a benign disease. So intralesional curettage with or without bone grafting is still the predominantly used therapy, but carries a risk of local recurrence of about 20% [3]. Phenol, introduced in 19th century medicine as carbolic acid, has long been used for achieving locally aseptic conditions or "sterilization" of remaining tumor cells after intralesional procedures as for example with giant cell tumor (GCT) of bone [16]. In a comparison of curettage with or without adjuvant phenolization in 43 versus 19 patients with ABC, the local recurrence rates were 14% vs. 16%, indicating that this adjuvans has no additional benefit [17]. This is confirmed by our present study. In GCT, the adjuvant effect of phenol is

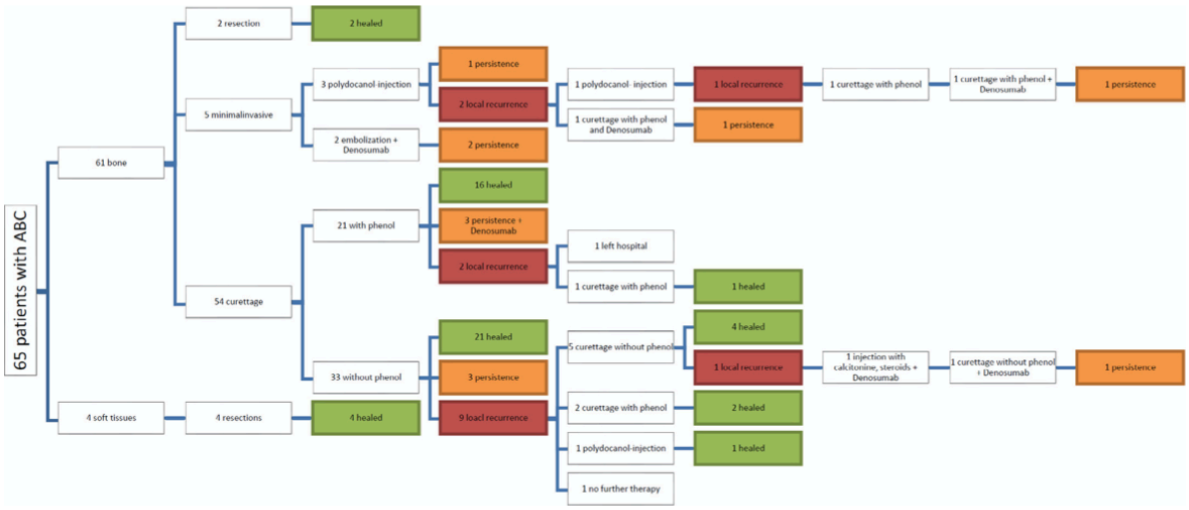

Fig. 2. Type of intervention and outcomes in 65 patients with ABC.

still a subject of discussion. Our own results using the same technique as in ABC showed a trend towards fewer recurrences but without achieving statistical significance [18]. In a recently published report by Nithyananth et al., the minimum time for effective action of phenol against giant cell tumour (GCT) cells was found to be 3 min (67% cell death) with 6 min being required for maximum efficacy (100% cell death) [19]. In our series, we used 50% phenol dissolved in 75% ethanol on swaps, maintained in the curettage cavity for 1 min. So this might have influenced the effect of the substance.

With high speed burring the same conflicting data is evident: no effect at all [17,20] or only one recurrence in 31 patients [21]. Argon beam coagulation, cryosurgery and cementation have either the risk of osteonecrosis and fracture or leave a biologically inert implant in a meta-epiphyseal location in children or young adults [10].

So over the years, less invasive procedures were propagated. Ethibloc, an alcoholic solution of a fibrogenic and thrombogenic agent proved to be effective with repeated injections but in some cases showed severe side effects [22]. In a randomized study with 94 patients, repeated injections of polidocanol showed better results than curettage alone (93% vs 85% healing) [23]. In our own series of patients presented here, polidocanol either led to local recurrence or to persistent disease.

Repeated arterial embolizations have also been reported with success rates of 80% and higher [12].

One group of investigators also described repeated injections of doxycycline, an antibiotic with some potential to inhibit matrix metalloproteinases and angiogenesis. Shiels et al. reported a healing rate of 94% with this method [24].

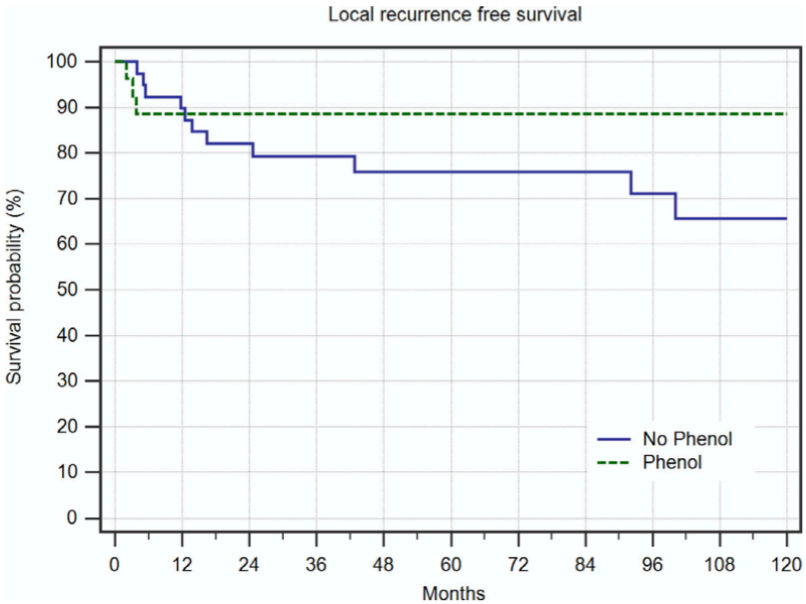

Fig. 3. Local recurrence free survival in 39 patients treated with curettage alone and 27 patients treated with curettage and adjuvant phenolization.

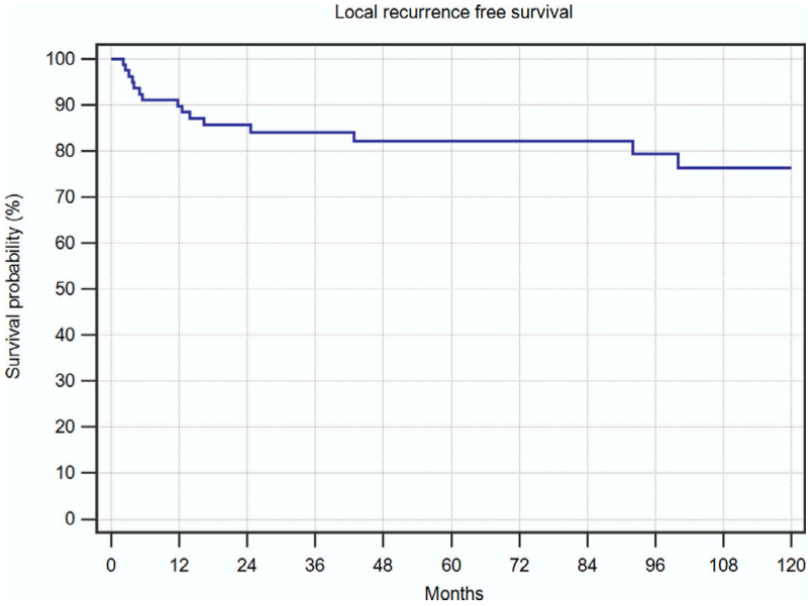

Fig. 4. Local recurrence free survival in 80 interventions in patients with ABC.

With a high rate of recalcification in GCT of bone, Denosumab, a human monoclonal antibody against the kappa B ligand (RANKL) which promotes osteoclast activation is also being used in ABC. In a recent case series of 9 patients, 5 were still under therapy, 2 patients had to be operated on and 2 patients showed stable disease after one and two years, respectively [15]. Our own experience is quite favorable. Two patients showed stable disease after cessation of Denosumab (Fig. 6), in 3 others, Denosumab was used after curettage. 2 patients showed stable small residual disease, one patient progressed and is again being treated with Denosumab. But we did also observed severe acute hypercalcemia following anti-RANKL withdrawal in children as described in several case reports [25].

5. Conclusion

Resection of aneurysmal bone cysts results in a local recurrence rate of 0% but is only feasible in very selected cases which is why curettage still represents the standard of treatment. Local recurrence does not depend on the use of adjuvant phenol as shown in this and other studies. Minimally invasive methods such as selective embolization and

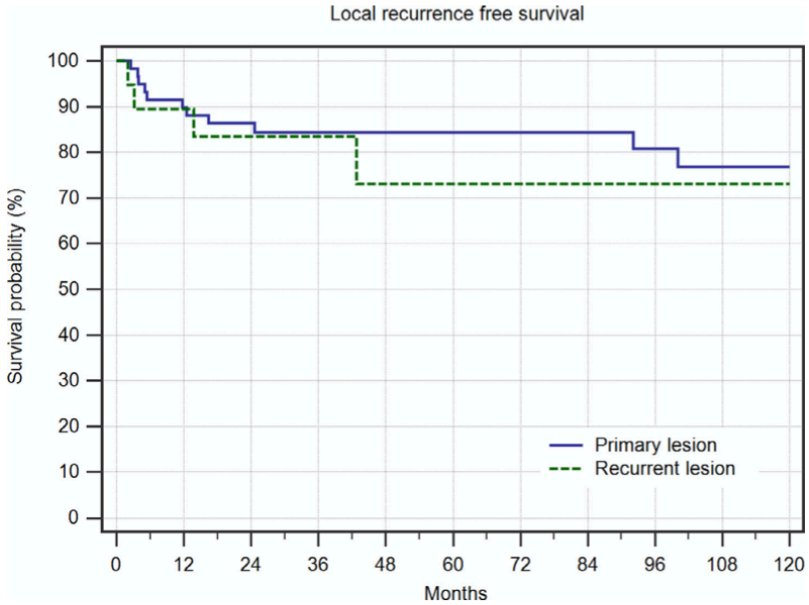

Fig. 5. Local recurrence free survival in 60 interventions in patients with primary ABC and 20 patients with recurrent ABC.

Table 1
A comparison of this data to published series of patients with primary aneurysmal bone cysts.

	Resection			Curettage			Polidocanol			Denosumab		
	CR	SD	PD	CR	SD	PD	CR	SD	PD	CR	SD	PD
This study	6 (100%)	0 (0%)	0 (0%)	44 (67%)	10 (15%)	12 (18%)	0 (0%)	1 (33%)	2 (67%)	0 (0%)	2 (100%)	0 (0%)
Basarir et al. [26]	19 (100%)	0 (0%)	0 (0%)	27 (77%)		8 (23%)						
Brosjö et al. [27]							37 (97%)		1 (3%)			
Dormans et al. [28]				37 (18%)		8 (82%)						
Erol et al. [29]	5 (100%)	0 (0%)	0 (0%)	52 (93%)		0 (0%)						
Flont et al. [30]	10 (100%)	0 (0%)	0 (0%)	14 (85%)		2 (15%)						
Gibbs et al. [31]	6 (100%)	0 (0%)	0 (0%)	30 (88%)		4 (12%)						
Kececi B. et al. [17]	9 (100%)	0 (0%)	0 (0%)	66 (87%)	0 (0%)	10 (13%)						
Kurucu et al. [32]										6 (67%)		3 (33%)
Kurucu et al. [32]										6 (67%)		3 (33%)
Mankin et al. [33]				120 (80%)		30 (20%)						
Palmerini et al. [15]										2 (22%)	7 (78%)	0 (0%)
Peeters et al. [34]				76 (95%)		4 (5%)						
Ramirez et al. [35]				21 (72%)		8 (28%)						
Rastogi et al. [36]							48 (67%)	22 (30%)	2 (3%)			
Reddy et al. [11]				162 (85%)		28 (15%)						
Schreuder et al. [34]				76 (95%		4 (5%)						
Schulte et al. [37]				33 (80%)		8 (20%)						
Shooshtarizadeh et al. [38]				33 (87%)	0 (0%)	5 (13%)						
Solooki et al. [39]	4 100%	0 (0%)	0 (0%)	30 (94%)	0 (0%)	2 (6%)						
Varshney et al. [23]				39 (85%)	0 (0%)	7 (15%)	42 (93%)	0 (0%)	3 (7%)			
Vergel De dios et al. [3]	17 (100%)	0 (0%)	0 (0%)	107 (79%)	0 (0%)	29 (21%)						
Wang et al. [21]				30 (97)	0 (0%)	1 (3%)						

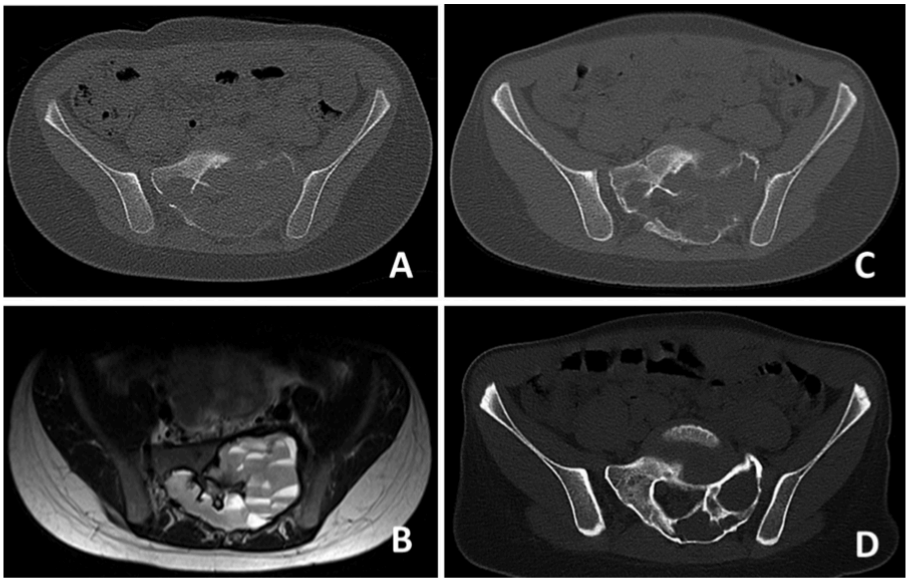

Fig. 6. CT-scan (A) showing massive osteolytic destruction of the sacrum at the levels S1 and S2 caused by ABC. (B) The lesions shows typical fluid- fluid levels on T2-weighted TSE imaging with the patient in supine position, which is a sign of internal bleeding within the cysts. (C) CT-scan two months after initiation of treatment with Denosumab showing initial sclerotic demarcation of the lesion and increased sclerosis. (D) CT-scan after one year of treatment demonstrating stable osseus reconstitution of both sacral ala.

injections of sclerosing agents or Doxycycline may result in healing or at least in tolerable persistence of residual lesions but require repetitive treatments and have so far not shown homogenous results between different institutions. Denosumab is a recent additional option especially in surgically critical locations such as the spine or the sacrum.

CRediT authorship contribution statement

Ferdinand Grahneis: Data curation, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Alexander Klein:** Methodology, Project administration, Writing - original draft, Writing - review & editing. **Andrea Baur-Melnyk:** Data curation, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Thomas Knösel:** Data curation, Investigation, Methodology, Validation, Visualization, Writing - original draft, Writing - review & editing. **Christof Birkenmaier:** Methodology, Project administration, Writing - original draft, Writing - review & editing. **Volkmar Jansson:** Methodology, Project administration, Writing - original draft, Writing - review & editing. **Hans Roland Dürr:** Data curation, Formal analysis,

Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all patients included in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Funding

This study did not have any grants or funding despite the academic setting of the institutions and authors.

Acknowledgements

Not applicable.

References

[1] H.L. Jaffe, L. Lichtenstein, Solitary unicameral bone cyst: with emphasis on the roentgen picture, the pathologic appearence and the pathogenesis, Arch. Surg. 44 (1942) 1004–1025.
[2] V. Martinez, H.A. Sissons, Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology, Cancer 61 (11) (1988) 2291–2304.
[3] A.M. Vergel De Dios, J.R. Bond, T.C. Shives, R.A. McLeod, K.K. Unni, Aneurysmal bone cyst. A clinicopathologic study of 238 cases, Cancer 69 (12) (1992) 2921–2931.
[4] R. Sciot, H. Dorfman, P. Brys, P. Dal Cin, I. De Wever, C.D. Fletcher, K. Jonson, N. Mandahl, F. Mertens, F. Mitelman, J. Rosai, A. Rydholm, I. Samson, G. Tallini, H. Van den Berghe, R. Vanni, H. Willen, Cytogenetic-morphologic correlations in aneurysmal bone cyst, giant cell tumor of bone and combined lesions. A report from the CHAMP study group, Mod. Pathol. 13 (11) (2000) 1206–1210.
[5] M.F. Pietschmann, A.M. Oliveira, M.M. Chou, S. Ihrler, M. Niederhagen, A. Baur-Melnyk, H.R. Durr, Aneurysmal bone cysts of soft tissue represent true neoplasms: a report of two cases, J. Bone Joint. Surg. Am. 93 (9) (2011) e45.
[6] J.R. Clough, C.H. Price, Aneurysmal bone cyst: pathogenesis and long term results of treatment, Clin. Orthop. Relat. Res. (97) (1973) 52–63.
[7] M.J. Kransdorf, D.E. Sweet, Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging, AJR Am. J. Roentgenol. 164 (3) (1995) 573–580.
[8] G. Panoutsakopoulos, N. Pandis, I. Kyriazoglou, P. Gustafson, F. Mertens, N. Mandahl, Recurrent t(16;17)(q22;p13) in aneurysmal bone cysts, Genes Chromosomes Cancer 26 (3) (1999) 265–266.
[9] D. Baumhoer, F. Amary, A.M. Flanagan, An update of molecular pathology of bone tumors. Lessons learned from investigating samples by next generation sequencing, Genes Chromosomes Cancer 58 (2) (2019) 88–99.
[10] H.Y. Park, S.K. Yang, W.L. Sheppard, V. Hegde, S.D. Zoller, S.D. Nelson, N. Federman, N.M. Bernthal, Current management of aneurysmal bone cysts, Curr. Rev. Musculoskelet. Med. 9 (4) (2016) 435–444.
[11] K.I. Reddy, F. Sinnaeve, C.L. Gaston, R.J. Grimer, S.R. Carter, Aneurysmal bone cysts: do simple treatments work? Clin. Orthop. Relat. Res. 472 (6) (2014) 1901–1910.
[12] G. Rossi, A.F. Mavrogenis, G. Facchini, T. Bartalena, E. Rimondi, M. Renzulli, A. Andreone, S. Durante, A. Angelini, C. Errani, How effective is embolization with N-2-butyl-cyanoacrylate for aneurysmal bone cysts? Int. Orthop. 41 (8) (2017) 1685–1692.
[13] S. Terzi, A. Gasbarrini, M. Fuiano, G. Barbanti Brodano, R. Ghermandi, S. Bandiera, S. Boriani, Efficacy and safety of selective arterial embolization in the treatment of aneurysmal bone cyst of the mobile Spine: a retrospective observational study, Spine (Phila Pa 1976) 42 (15) (2017) 1130–1138.
[14] F. Batisse, A. Schmitt, T. Vendeuvre, D. Herbreteau, C. Bonnard, Aneurysmal bone cyst: a 19-case series managed by percutaneous sclerotherapy, Orthop. Traumatol. Surg. Res. 102 (2) (2016) 213–216.
[15] E. Palmerini, P. Ruggieri, A. Angelini, S. Boriani, D. Campanacci, G.M. Milano, M. Cesari, A. Paioli, A. Longhi, M.E. Abate, G. Scoccianti, S. Terzi, G. Trovarelli, A. Franchi, P. Picci, S. Ferrari, M.P. Leopardi, M. Pierini, Denosumab in patients with aneurysmal bone cysts: a case series with preliminary results, Tumori. 104 (5) (2018) 344–351.
[16] R. Capanna, A. Sudanese, N. Baldini, M. Campanacci, Phenol as an adjuvant in the control of local recurrence of benign neoplasms of bone treated by curettage, Ital. J. Orthop. Traumatol. 11 (3) (1985) 381–388.
[17] B. Kececi, L. Kucuk, A. Isayev, D. Sabah, Effect of adjuvant therapies on recurrence in aneurysmal bone cysts, Acta Orthop. Traumatol. Turc. 48 (5) (2014) 500–506.
[18] M.F. Pietschmann, R.A. Dietz, S. Utzschneider, A. Baur-Melnyk, V. Jansson, H.R. Durr, The influence of adjuvants on local recurrence rate in giant cell tumour of the bone, Acta Chir. Belg. 110 (6) (2010) 584–589.
[19] M. Nithyananth, A.J. Priscilla, P.V. Boopalan, V.T. Titus, V.N. Lee, Time required for effective action of phenol against giant cell tumour cells, J. Orthop. Surg. (Hong Kong) 22 (1) (2014) 104–107.
[20] W.C. Lin, H.T. Wu, C.J. Wei, C.Y. Chang, Aneurysmal bone cyst arising from fibrous dysplasia of the frontal bone (2004:2b), Eur. Radiol. 14 (5) (2004) 930–932.
[21] E.H. Wang, M.L. Marfori, M.V. Serrano, D.A. Rubio, Is curettage and high-speed burring sufficient treatment for aneurysmal bone cysts? Clin. Orthop. Relat. Res. 472 (11) (2014) 3483–3488.
[22] V. Topouchian, K. Mazda, B. Hamze, J.D. Laredo, G.F. Pennecot, Aneurysmal bone cysts in children: complications of fibrosing agent injection, Radiology 232 (2) (2004) 522–526.
[23] M.K. Varshney, S. Rastogi, S.A. Khan, V. Trikha, Is sclerotherapy better than intralesional excision for treating aneurysmal bone cysts? Clin. Orthop. Relat. Res. 468 (6) (2010) 1649–1659.
[24] W.E. Shiels 2nd, A.C. Beebe, J.L. Mayerson, Percutaneous doxycycline treatment of juxtaphyseal aneurysmal bone cysts, J. Pediatr. Orthop. 36 (2) (2016) 205–212.
[25] S. Roux, M.H. Massicotte, L. Huot Daneault, L. Brazeau-Lamontagne, J. Dufresne, Acute hypercalcemia and excessive bone resorption following anti-RANKL withdrawal: case report and brief literature review, Bone 120 (2019) 482–486.
[26] K. Basarir, A. Piskin, B. Guclu, Y. Yildiz, Y. Saglik, Aneurysmal bone cyst recurrence in children: a review of 56 patients, J. Pediatr. Orthop. 27 (8) (2007) 938–943.
[27] O. Brosjo, P. Pechon, A. Hesla, P. Tsagozis, H. Bauer, Sclerotherapy with polidocanol for treatment of aneurysmal bone cysts, Acta Orthop. 84 (5) (2013) 502–505.
[28] J.P. Dormans, B.G. Hanna, D.R. Johnston, J.S. Khurana, Surgical treatment and recurrence rate of aneurysmal bone cysts in children, Clin. Orthop. Relat. Res. 421 (2004) 205–211.
[29] B. Erol, M.O. Topkar, E. Caliskan, R. Erbolukbas, Surgical treatment of active or aggressive aneurysmal bone cysts in children, J. Pediatr. Orthop. B 24 (5) (2015) 461–468.
[30] P. Flont, M. Kolacinska-Flont, K. Niedzielski, A comparison of cyst wall curettage and en bloc excision in the treatment of aneurysmal bone cysts, World J. Surg. Oncol. 11 (2013) 109.
[31] C.P. Gibbs Jr., M.C. Hefele, T.D. Peabody, A.G. Montag, V. Aithal, M.A. Simon, Aneurysmal bone cyst of the extremities. Factors related to local recurrence after curettage with a high-speed burr, J. Bone Joint Surg. Am. 81 (12) (1999) 1671–1678.
[32] N. Kurucu, C. Akyuz, F.B. Ergen, B. Yalcin, K. Kosemehmetoglu, M. Ayvaz, A. Varan, B. Aydin, T. Kutluk, Denosumab treatment in aneurysmal bone cyst: Evaluation of nine cases, Pediatr. Blood Cancer 65 (4) (2018).
[33] H.J. Mankin, F.J. Hornicek, E. Ortiz-Cruz, J. Villafuerte, M.C. Gebhardt, Aneurysmal bone cyst: a review of 150 patients, J. Clin. Oncol. 23 (27) (2005) 6756–6762.
[34] S.P. Peeters, I.C. Van der Geest, J.W. de Rooy, R.P. Veth, H.W. Schreuder, Aneurysmal bone cyst: the role of cryosurgery as local adjuvant treatment, J. Surg. Oncol. 100 (8) (2009) 719–724.
[35] A.R. Ramirez, R.P. Stanton, Aneurysmal bone cyst in 29 children, J. Pediatr. Orthop. 22 (4) (2002) 533–539.
[36] S. Rastogi, M.K. Varshney, V. Trikha, S.A. Khan, B. Choudhury, R. Safaya, Treatment of aneurysmal bone cysts with percutaneous sclerotherapy using polidocanol. A review of 72 cases with long-term follow-up, J. Bone Joint Surg. Br. 88 (9) (2006) 1212–1216.
[37] M. Schulte, M.R. Sarkar, A. Von Baer, M. Schultheiss, G. Suger, E. Hartwig, Therapy of aneurysmal bone cyst, Unfallchirurg 103 (2) (2000) 115–121.
[38] T. Shooshtarizadeh, S. Movahedinia, H. Mostafavi, K. Jamshidi, S.H. Sami, Aneurysmal bone cyst: an analysis of 38 cases and report of four unusual surface ones, Arch. Bone Jt. Surg. 4 (2) (2016) 166–172.
[39] S. Solooki, Y. Keikha, A.R. Vosoughi, Can ethanol be used as an adjuvant to extended curettage in order to reduce the recurrence rate of aneurysmal bone cyst? Rev. Bras. Ortop. 52 (3) (2017) 349–353.

Dürr *et al. BMC Musculoskeletal Disorders* (2019) 20:456
https://doi.org/10.1186/s12891-019-2855-y

BMC Musculoskeletal Disorders

CASE REPORT Open Access

Aneurysmal bone cyst: results of an off label treatment with Denosumab

Hans Roland Dürr[1*], Ferdinand Grahneis[1], Andrea Baur-Melnyk[2], Thomas Knösel[3], Christof Birkenmaier[1], Volkmar Jansson[1] and Alexander Klein[1]

Abstract

Background: The treatment of aneurysmal bone cysts (ABCs) has evolved and less invasive methods have been tried. Denosumab is a monoclonal antibody which inhibits osteoclasts. It has been shown to be effective in giant cell tumour of bone (GCT) of bone and hence promises some effect also in ABC. We report on 6 patients treated with Denosumab and compare our results to the cases already published.

Methods: Data of 6 patients with ABCs and patients whose treatment included Denosumab were retrospectively analyzed. Denosumab was used at a dose of 120 mg on days 1, 8, 15 and 29, and every 4 weeks thereafter. In some of these patients the dose was reduced at the end of the treatment. Clinical and radiological responses were evaluated.

Results: In 4 female and 2 male patients with a mean age of 17 years (range: 6–30 years) the lesions were located in the sacrum (2), in distal radius, distal femur, talus and pelvis. One of the sacral lesions healed after 12 months and has stayed stable for 3 years since. The second patient received 2 years of therapy with recalcification, but recurred 1 year later and is under renewed therapy. The pelvic lesion improved but recurred. This patient has a 13-years history of intermittent therapy including surgery, two pregnancies and remains in a stable situation. The lesion of the talus did not improve with Denosumab after surgery and was complicated by destruction of the ankle joint with osteoarthritis. Recurrent lesions of the distal femur and the distal radius, previously treated by curettage and bone grafting healed under Denosumab and have remained stable for 2 and 3 years, respectively. One case of severe hypercalcemia was observed in a 7-year old child 6 months after discontinuation of Denosumab.

Conclusion: Denosumab provides a treatment option for ABCs in anatomically critical locations. Adjuvant application might reduce the rate of local recurrence. In young patients, severe rebound hypercalcemia months after discontinuation of Denosumab may occur.

Keywords: Aneurysmal bone cyst, Denosumab, Recurrence, Prognosis

Background

Aneurysmal bone cysts (ABC) are considered benign yet locally aggressive lesions with a relevant potential for local recurrence. They typically appear in the metaphyses of the long bones and in the vertebral column and were first described by Jaffe and Liechtenstein in 1942 [1–3]. ABC's are most often seen in children and young adults with no gender predilection. They are lytic, blood-filled, separated by fibrous septa and with histopathology typically showing fibroblasts, osteoclast-type giant cells and reactive woven bone [4].

ABC(s) were originally thought to be reactive in nature, caused by a circulatory abnormality leading to an increased venous pressure and resulting in dilation of the intraosseous vascular network [5, 6]. In 1999, Panoutsakopoulos et al. demonstrated a balanced chromosomal translocation t(16;17)(q22;p13) as a cytogenetic abnormality in primary aneurysmal bone cyst [7] involving the ubiquitin carboxyl-terminal hydrolase 6 (USP6) gene, located on chromosome 17p13. Since then, the neoplastic nature of ABC has been established and the USP6 translocation has since been found in approximately 75% of cases [8]. In differentiating primary

* Correspondence: hans_roland.duerr@med.uni-muenchen.de
[1]Orthopaedic Oncology, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Marchioninistr. 15, D-81377 Munich, Germany
Full list of author information is available at the end of the article

ABC's from secondary lesions or other tumors such as telangiectatic osteosarcoma this may be an option in selected cases. This particular translocation enhances the production of TRE17, a protease which leads to increased matrix metalloproteinase (MMP)-9 and increased MMP-10 activity [9]. This in turn is associated not only with blocking osteoblastic maturation via an autocrine mechanism involving bone morphogenetic dysregulation, but also increased release of VEGF (Vascular Endothelial Growth Factor) thus enhancing vascularization [10].

The treatment of ABC has changed over the years. Due to its often mutilating character, resection is not an acceptable option in most of the cases leaving intralesional procedures such as curettage as the standard of care [11]. Less invasive methods such as aggressive biopsy ("Curopsy") [12], selective arterial embolization [13, 14], sclerotherapy with ethibloc or polidocanol [15] have been tried.

Denosumab is a human monoclonal antibody which binds specifically to the cytokine receptor activator of nuclear factor-kappa B ligand (RANKL) [16]. This prevents RANKL from activating the RANK receptor of osteoclasts, inhibiting osteoclast function. Denosumab is highly effective in giant cell tumour of bone (GCT) and therefore similar effects in principle could be hoped for in ABC, which has distinct similarities to GCT [17]. Up to now no protocol or treatment recommendation for the use of denosumab in ABC exists.

To our best knowledge, 2 case series (with 9 patients each) have previously been published [18–20] with an additional 11 cases having been published as individual case reports [20–29].

The aim of this study is to report our results from a series of 6 patients and to compare our experience to the data already published.

Methods

Retrospectively all 65 patients with ABCs treated at our institution between 1982 and 2014 were analyzed with data having been collected in a prospective fashion. In 6 cases, Denosumab was used off-label in accordance to the established protocol in giant cell tumor (GCT) of bone [30]. The indications had been expected unreasonable morbidity of surgical treatment either in a primary or in a recurrent lesion or in an adjuvant setting after surgery for local recurrence. This study was approved by the ethics committee of our faculty (#18–373). Written consent was obtained from all patients included in this study. Denosumab was administered subcutaneously at a dose of 120 mg on days 1, 8, 15 and 29, and every 4 weeks afterwards. This scheme is later referred to as the so-called adult regimen. In a 6-year old boy, the dose was reduced as is described below. In some of the patients, the dose was reduced towards the end of the treatment as also described below. Calcium 500 mg and Vitamin D 1000 IU were supplemented on a daily basis. Clinical data was collected from the patients charts. Routine follow-up investigations such as magnetic resonance imaging (MRI) or radiographs and in specific cases also computed tomography (CT) were performed every 3 months in the first year of therapy, every 6 months in the second year and then based on individual decision. But as described in the literature ABCs should be considered as completely healed if recurrence does not occur within 2 years after the end of therapy [13].

Results

From 2011 to 2018, 6 patients (4 female and 2 male) with histologically proven ABCs were treated with Denosumab. The mean age was 17 years (range: 6–30 years). Two lesions were located in the sacrum, one each in distal radius, distal femur, talus and pelvis. Pain was the leading symptom in all patients with a mean duration of 14 months (1–42 months) prior to diagnosis.

The two patients with sacral ABCs underwent needle biopsies prior to initiating treatment.

Case 1

In this 6-year-old boy, the Denosumab dosage regimen was adapted from a published trial of Densoumab in GCT by using 50% of the proposed adult dosage (60 mg every 4 weeks with two additional doses on days 8 and 15). Two months after the initiation of treatment the child was free of pain. A second CT-scan showed the ABC constant in size but with increasing bone density at the margins of the lesion (Fig. 1). At this point, the parents requested an additional embolization, but angiography showed no tumour vessels and no arterial irregularities and only a minimal embolization with 0.5 ml silicon spheres was performed. The Denosumab application was continued. After 1 year of treatment, the child was free of pain with normal growth and teething. The latest CT-scan showed an impressive growth of bone starting from the margins of the lesion with remnants of the cyst on the left and with complete filling of the defect on the right side. The treatment was stopped and a follow-up examination was scheduled for 12 months later. In October 2015, another CT scans showed nearly complete healing of the cyst. But as a consequence of Denosumab discontinuation, a severe rebound hypercalcemia had developed 6 months after the end of therapy and made intensive care treatment necessary.

Case 2

An 18-year old male, also with a sacral ABC had an injection with polidocanol and an embolization not leading to any improvement. Three months later, Denosumab was initiated using the above mentioned adult regimen. After 1 year with clinical and radiological success, the dosage was gradually reduced and after 2 years Denosumab was

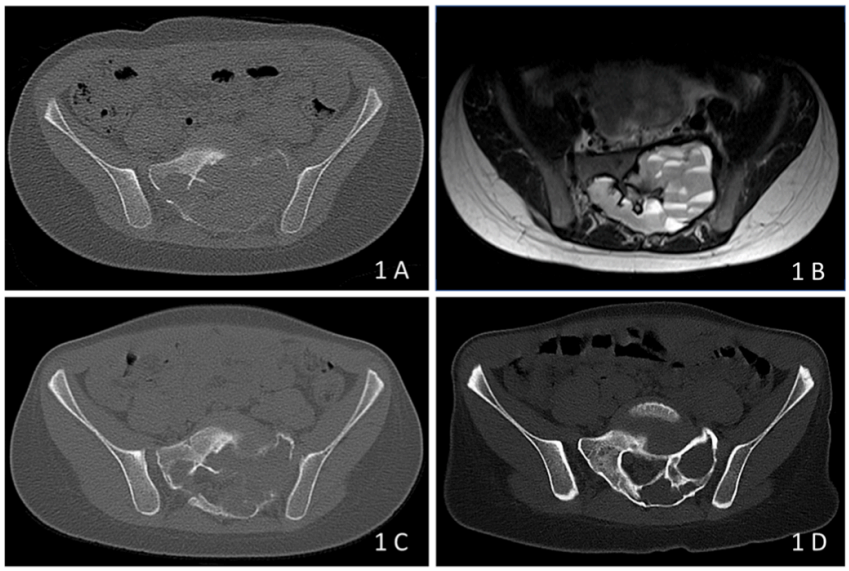

Fig. 1 **a**, **b**: CT-scan (A) showing the massive destruction of the left and also in parts the right sacrum at the levels S1 and S2. The blood filling of the cyst is clearly visible as fluid-fluid levels in the T2-weighted MRI image (**b**). **c**: CT-scan 2 months after initiation of treatment showing increasing bone density at the margins of the lesion. **d**: CT-scan one after 1 year of treatment proofing the total bone restoration in the right and the impressive gain of bone at the left sacrum

stopped. One year later he developed a local recurrence as evidenced by MRI and Denosumab was restarted. 1 ½ year later with again radiologically confirmed recalcification the dosage was again reduced.

Case 3

A 30-year old lady with a very large ABC of the left pelvis had curettage and bone grafting after CT-guided biopsy and developed a recurrence 1 year later. Again curettage and bone grafting was performed resulting in a second recurrence, 3 ½ year later. Denosumab was then initiated using the adult regimen. After 5 months, a clear response was documented, but after 8 months despite Denosumab, local recurrence was evident and due to the reduced stability around the acetabulum, curettage and bone grafting were again performed. Three months later, she became pregnant and 1 1/2 years after the previous surgery, another recurrence was seen and Denosumab was restarted after cessation of breast feeding 5 months after the diagnosis of LR. After 18 months, the situation was stable and the patient decided for a second pregnancy with cessation of Denosumab. Three years later and after an uncomplicated second pregnancy with twins, a recurrence was again obvious. A needle biopsy was performed that excluded GCT and confirmed ABC. Denosumab was started again resulting in partial sclerosing of the lesion. The dosage of Denosumab has since been reduced to 120 mg every 2 months.

Case 4

In a 16-year old female after a second recurrence at the talus treated with bone grafting, Denosumab was used for 1 year with 120 mg per month leading to a stable situation. Two years later the lesion again recurred but now as a ganglioma due to the secondary destruction of the joint surface. In order to preserve all options for future treatment of the ankle joint, repeat curettage and bone grafting were performed.

Case 5

In a 15-year old female the lesion at the distal radius was treated with polidocanol injections and a simultaneous biopsy at the time of the first injection. Due to progression subsequently curettage and bone grafting were performed. Three months later due to recurrence the procedure had to be repeated (Fig. 2). Denosumab was then initiated in the adult regimen for 6 months leading to healing of the lesion with the latest follow-up now 3 years after that point.

Case 6

In a 16-year old female after biopsy the lesion at the distal femur was treated with an embolization that had no effect and resulted in further growth of the cyst. Curettage and bone grafting were performed showing progressive local recurrence 3 and 5 months after surgery. Denosumab was begun according to the adult regimen for 1 year followed by 120 mg every 2 months for 6 months and by 120 mg

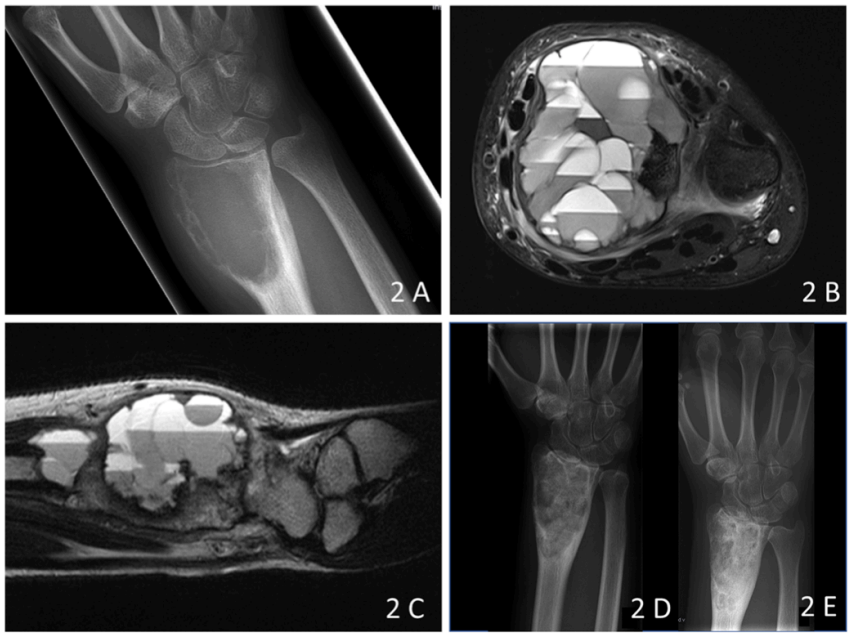

Fig. 2 a Radiograph of the right distal radius showing the typical metaepiphyseal exentric osteolysis of an ABC of bone. **b**: The lesions shows typical fluid- fluid levels on T2-weighted TSE imaging with the patient in supine position. **c:** Local recurrence 3 months after curettage and bone grafting. **d**, **e**: Radiographs 2 months (**d**) and 1 year (**e**) after surgery and starting of Denosumab therapy

every 3 months for another 6 months. Under this therapy, the lesion healed without any signs of recurrence and has been stable now for 2 years.

So in total Denosumab healed one sacral lesion and stabilized a second with recurrence after cessation and recalcification after re-establishment of therapy. The pelvic lesion improved but recurred after cessation of therapy. This particular patient has a 13-years history of intermittent treatment with two pregnancies in between and is currently in a stable situation. The lesion of the talus did not improve but was complicated by secondary osteoarthritic destruction. The recurrencies of the distal femoral and the distal radius lesion after curettage and bone grafting healed with Denosumab and have remained s for 2 and 3 years after cessation of therapy.

Discussion

ABC are benign but locally aggressive lesions. Wide resection is not an option for the majority of patients because of the resulting disability. So intralesional curettage with or without bone grafting is still the predominantly used therapy, but carries a risk of local recurrence of about 20% [3]. Over the years, less invasive procedures have been propagated. Ethibloc, an alcoholic solution of a fibrogenic and thrombogenic agent proved to be effective with repeated injections but in some cases showed severe side effects [31]. In a randomized study with 94 patients, repeated injections of polidocanol showed better results than curettage alone (93% vs 85% healing) [32]. Repeated arterial embolizations have also been reported with success rates of more than 80% [13]. Also, repeated injections of doxycycline, an antibiotic with some potential to inhibit matrix metalloproteinases and angiogenesis was reported by Shiels et al. with a healing rate of 94% in their series [33]. An overview comparing the results of different forms of therapy including our own patients treated without Denosumab has recently been published [34].

In GCT the interaction of RANK and RANKL is an important factor which regulates the giant cell formation and progression of this tumor [35]. The pathophysiology of ABC seems to be similar to this [29, 36]. Denosumab, which effectively blocks interaction between RANKL and RANK has been approved for the treatment of osteoporosis, metastatic bone disease, multiple myeloma and GCT [19, 37]. The use of denosumab as an adjuvant treatment in patients with GCT has shown a high rate of recalcification [38].

In ABC the first report of Denosumab treatment dates back to 2012 [20]. Later 11 cases had been described in 9 studies. All patients showed regression of the lesion and recalcification. This treatment effect rendered surgery possible in two cases and the lesions were resected. The reported follow-up was rather inhomogenous with between 0 and 19 months after cessation of Denosumab. Local recurrence was described in just one case [21].

Kurucu et al. described 9 patients, 3 of them with surgical or non-surgical pretreatment [19]. Denosumab was given

for 6–14 months with median 15 doses. All patients were free of symptoms after 3 months. Radiological improvement was evident in 8 cases. Follow-up time after the end of treatment was 10–24 months (median 15 months). 2 patients had further surgery, two other patients developed recurrence (after 16 months) or progressive disease and had renewed treatment with Denosumab or surgery. In total, the authors reported recurrence or progression in 4 of the 9 patients. In addition, they observed severe hypercalcemia in two patients 10 and 24 months after cessation of treatment.

Palmerini et al. reported 9 patients with Denosumab treatment [18]. It is not clear from their publication how many of the patients had any kind of prior therapy. Two patients had surgery after Denosumab. All 9 patients were classified as having sustained tumor control. At the last follow-up 5 patients were still on Denosumab treatment, 2 patients were disease-free after curettage and 2 patients are now 12 and 24 months without Denosumab and free of disease. No patient developed severe side effects.

Denosumab is effective in ABC as it is in GCT of bone. Our own results are similar to those described in both previously published case series. It is clear from those series as as well as from our own cases, that follow-up time after cessation of treatment is a major factor because recurrence, with some exceptions, needs time to develop. In this respect, the published cases may report better results than might be observed with longer follow-up. In general, all published cases demonstrated a clear clinical and radiological benefit of Denosumab in more than two thirds of the patients.

A major factor is the age of the patients. ABC is a lesion in young adults or children. The published series include patients as young as 2 years [19]. There is a risk of retardation in growth and disturbed dental developing with Denosumab not very well described up to now. The currently available knowledge is mainly based on individual treatment results in children suffering from fibrous dysplasia or osteogenesis imperfecta [39–43].

Most serious and as described also in one of our own patients is a rapid loss of the newly acquired bone caused by rebound formation and activation of osteoclasts once treatment is stopped, resulting in severe hypercalcemia [44, 45]. Other known adverse effects during denosumab therapy are hypocalcemia, necrosis of the jaw, fatigue, muscular pain or atypical femoral fractures if longer used [38].

Conclusions

Denosumab provides an additional non-invasive method of treating ABCs in surgically critical locations such as the spine or the pelvis. As shown here, it may also reduce the rate of local recurrence with adjuvant application after intralesional surgery in aggressive lesions. Care providers need to be aware that the use of Denosumab in ABC is off-label and therefore requires a thorough interdisciplinary discussion with the patient or his/her family. The most common severe complication of Denosumab, osteonecrosis of the jaw, has not been described up to now in patients treated for ABC. But due to the low age of many of the children, severe rebound hypercalcemia months after cessation of therapy remains a considerable risk and implies that consequent laboratory follow-up for at least 2 years be performed.

Abbreviations

ABC: Aneurysmal bone cyst; CT: Computed tomography; GCT: Giant cell tumour; IU: International Units; mg: Milligramms; MMP: Metalloproteinase; MRI: Magnetic resonance imaging; RANK: Cytokine receptor activator of nuclear factor-kappa B; RANKL: Cytokine receptor activator of nuclear factor-kappa B ligand; USP6: Ubiquitin carboxyl-terminal hydrolase 6; VEGF: Vascular endothelial growth factor

Acknowledgements

Not applicable.

Authors' contributions

HRD Corresponding and senior author. Study concept, data analysis, key clinical perspective, main manuscript preparation. FG MD degree Student on ABC. Patient management and data collection. AB Radiologist reviewing the radiologic investigations. TK Pathologist reviewing all histological investigations. CB Surgeon, manuscript preparation. VJ Surgeon, manuscript preparation. AK Surgeon, manuscript preparation. Each author has contributed significantly to, and is willing to take public responsibility for this study: its design, data acquisition, and analysis and interpretation of data. All authors have been actively involved in the drafting and critical revision of the manuscript. All authors had read and approved the final manuscript.

Funding

This study was not supported by any dedicated grants or funding.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Medical Faculty, University of Munich. Written consent was obtained from all patients or from the parents of the participants under 16 years of age included in this study.

Consent for publication

All patients or the parents of the participants under 16 years of age included in this study gave consent for publishing their clinical details along with any radiological images to be published in this study.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Orthopaedic Oncology, Department of Orthopaedics, Physical Medicine and Rehabilitation, University Hospital, LMU Munich, Marchioninistr. 15, D-81377 Munich, Germany. [2]Department of Radiology, University Hospital, LMU Munich, Munich, Germany. [3]Institute of Pathology, University Hospital, LMU Munich, Munich, Germany.

Received: 13 May 2019 Accepted: 27 September 2019
Published online: 20 October 2019

References

1. Jaffe HL, Lichtenstein L. Solitary unicameral bone cyst: with emphasis on the roentgen picture, the pathologic appearence and the pathogenesis. Arch Surg. 1942;44:1004–25.

2. Martinez V, Sissons HA. Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology. Cancer. 1988;61(11):2291–304.
3. Vergel De Dios AM, Bond JR, Shives TC, McLeod RA, Unni KK. Aneurysmal bone cyst. A clinicopathologic study of 238 cases. Cancer. 1992;69(12):2921–31.
4. Sciot R, Dorfman H, Brys P, Dal Cin P, De Wever I, Fletcher CD, Jonson K, Mandahl N, Mertens F, Mitelman F, et al. Cytogenetic-morphologic correlations in aneurysmal bone cyst, giant cell tumor of bone and combined lesions. A report from the CHAMP study group. Mod Pathol. 2000;13(11):1206–10.
5. Clough JR, Price CH. Aneurysmal bone cyst: pathogenesis and long term results of treatment. Clin Orthop Relat Res. 1973;97:52–63.
6. Kransdorf MJ, Sweet DE. Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging. AJR Am J Roentgenol. 1995;164(3):573–80.
7. Panoutsakopoulos G, Pandis N, Kyriazoglou I, Gustafson P, Mertens F, Mandahl N. Recurrent t(16;17)(q22;p13) in aneurysmal bone cysts. Genes Chromosomes Cancer. 1999;26(3):265–6.
8. Baumhoer D, Amary F, Flanagan AM. An update of molecular pathology of bone tumors. Lessons learned from investigating samples by next generation sequencing. Genes Chromosomes Cancer. 2019;58(2):88–99.
9. Ye Y, Pringle LM, Lau AW, Riquelme DN, Wang H, Jiang T, Lev D, Welman A, Blobel GA, Oliveira AM, et al. TRE17/USP6 oncogene translocated in aneurysmal bone cyst induces matrix metalloproteinase production via activation of NF-kappaB. Oncogene. 2010;29(25):3619–29.
10. Lau AW, Pringle LM, Quick L, Riquelme DN, Ye Y, Oliveira AM, Chou MM. TRE17/ubiquitin-specific protease 6 (USP6) oncogene translocated in aneurysmal bone cyst blocks osteoblastic maturation via an autocrine mechanism involving bone morphogenetic protein dysregulation. J Biol Chem. 2010;285(47):37111–20.
11. Park HY, Yang SK, Sheppard WL, Hegde V, Zoller SD, Nelson SD, Federman N, Bernthal NM. Current management of aneurysmal bone cysts. Curr Rev Musculo Med. 2016;9(4):435–44.
12. Reddy KI, Sinnaeve F, Gaston CL, Grimer RJ, Carter SR. Aneurysmal bone cysts: do simple treatments work? Clin Orthop Relat Res. 2014;472(6):1901–10.
13. Rossi G, Mavrogenis AF, Facchini G, Bartalena T, Rimondi E, Renzulli M, Andreone A, Durante S, Angelini A, Errani C. How effective is embolization with N-2-butyl-cyanoacrylate for aneurysmal bone cysts? Int Orthop. 2017;41(8):1685–92.
14. Terzi S, Gasbarrini A, Fuiano M, Barbanti Brodano G, Ghermandi R, Bandiera S, Boriani S. Efficacy and safety of selective arterial embolization in the treatment of aneurysmal bone cyst of the Mobile spine: a retrospective observational study. Spine (Phila Pa 1976). 2017;42(15):1130–8.
15. Batisse F, Schmitt A, Vendeuvre T, Herbreteau D, Bonnard C. Aneurysmal bone cyst: a 19-case series managed by percutaneous sclerotherapy. Orthop Traumatol Surg Res. 2016;102(2):213–6.
16. Bekker PJ, Holloway DL, Rasmussen AS, Murphy R, Martin SW, Leese PT, Holmes GB, Dunstan CR, DePaoli AM. A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. J Bone Miner Res. 2004;19(7):1059–66.
17. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. Curr Opin Oncol. 2012;24(4):397–403.
18. Palmerini E, Ruggieri P, Angelini A, Boriani S, Campanacci D, Milano GM, Cesari M, Paioli A, Longhi A, Abate ME, et al. Denosumab in patients with aneurysmal bone cysts: a case series with preliminary results. Tumori. 2018;104(5):344–51.
19. Kurucu N, Akyuz C, Ergen FB, Yalcin B, Kosemehmetoglu K, Ayvaz M, Varan A, Aydin B, Kutluk T. Denosumab treatment in aneurysmal bone cyst: Evaluation of nine cases. Pediatr Blood Cancer. 2018;65(4):e26926. https://doi.org/10.1002/pbc.26765.
20. Lange T, Stehling C, Frohlich B, Klingenhofer M, Kunkel P, Schneppenheim R, Escherich G, Gosheger G, Hardes J, Jurgens H, et al. Denosumab: a potential new and innovative treatment option for aneurysmal bone cysts. Eur Spine J. 2013;22(6):1417–22.
21. Pauli C, Fuchs B, Pfirrmann C, Bridge JA, Hofer S, Bode B. Response of an aggressive periosteal aneurysmal bone cyst (ABC) of the radius to denosumab therapy. World J Surg Oncol. 2014;12:17.
22. Dubory A, Missenard G, Domont J, Court C. Interest of Denosumab for the treatment of Giant-cells tumors and aneurysmal bone cysts of the spine. About Nine Cases. Spine (Phila Pa 1976). 2016;41(11):E654–60.
23. Fontenot PB, Jesurajan J, Bui M, Reed D, Binitie O. Recurrent aneurysmal bone cyst of the distal fibula treated with Denosumab and curettage. Case Rep Oncol Med. 2018;2018:1574343.
24. Asi KW, Abdelmeguid A, Bell D, Hanna EY. Massive aneurysmal bone cyst of the skull base treated with denosumab. Head Neck. 2018;40(12):E107–e113.
25. Ghermandi R, Terzi S, Gasbarrini A, Boriani S. Denosumab: non-surgical treatment option for selective arterial embolization resistant aneurysmal bone cyst of the spine and sacrum. Case report. Eur Rev Med Pharmacol Sci. 2016;20(17):3692–5.
26. Patel RS, Dhamne CA, Gopinathan A, Kumar N, Kumar N. Denosumab: a potential treatment option for aneurysmal bone cyst of the atlas. Eur Spine J. 2018;27(Suppl 3):494–500.
27. Ntalos D, Priemel M, Schlickewei C, Thiesen DM, Rueger JM, Spiro AS. Therapeutic Management of a Substantial Pelvic Aneurysmatic Bone Cyst Including the off-label use of Denosumab in a 35-year-old female patient. Case Rep Ortho. 2017;2017:9125493.
28. Skubitz KM, Peltola JC, Santos ER, Cheng EY. Response of aneurysmal bone cyst to Denosumab. Spine (Phila Pa 1976). 2015;40(22):E1201–4.
29. Pelle DW, Ringler JW, Peacock JD, Kampfschulte K, Scholten DJ 2nd, Davis MM, Mitchell DS, Steensma MR. Targeting receptor-activator of nuclear kappaB ligand in aneurysmal bone cysts: verification of target and therapeutic response. Transl Res. 2014;164(2):139–48.
30. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, Roudier M, Smith J, Ye Z, Sohn W, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol. 2010;11(3):275–80.
31. Topouchian V, Mazda K, Hamze B, Laredo JD, Pennecot GF. Aneurysmal bone cysts in children: complications of fibrosing agent injection. Radiology. 2004;232(2):522–6.
32. Varshney MK, Rastogi S, Khan SA, Trikha V. Is sclerotherapy better than intralesional excision for treating aneurysmal bone cysts? Clin Orthop Relat Res. 2010;468(6):1649–59.
33. Shiels WE 2nd, Beebe AC, Mayerson JL. Percutaneous doxycycline treatment of Juxtaphyseal aneurysmal bone cysts. J Pediatr Orthop. 2016;36(2):205–12.
34. Grahneis F, Klein A, Baur-Melnyk A, Knösel T, Birkenmaier C, Jansson V, Dürr HR. Aneurysmal bone cyst: a review of 65 patients. J Bone Oncol. 2019;18:100255. https://doi.org/10.1016/j.jbo.2019.100255.
35. Wu PF, Tang JY, Li KH. RANK pathway in giant cell tumor of bone: pathogenesis and therapeutic aspects. Tumour Biol. 2015;36(2):495–501.
36. Won KY, Kalil RK, Kim YW, Park YK. RANK signalling in bone lesions with osteoclast-like giant cells. Pathology. 2011;43(4):318–21.
37. Savvidou OD, Bolia IK, Chloros GD, Papanastasiou J, Koutsouradis P, Papagelopoulos PJ. Denosumab: current use in the treatment of primary bone tumors. Orthopedics. 2017;40(4):204–10.
38. Luengo-Alonso G, Mellado-Romero M, Shemesh S, Ramos-Pascua L, Pretell-Mazzini J. Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature. Arch Orthop Trauma Surg. 2019;139(10):1339–49.
39. Boyce AM. Denosumab: an emerging therapy in pediatric bone disorders. Curr Osteoporos Rep. 2017;15(4):283–92.
40. Wang HD, Boyce AM, Tsai JY, Gafni RI, Farley FA, Kasa-Vubu JZ, Molinolo AA, Collins MT. Effects of denosumab treatment and discontinuation on human growth plates. J Clin Endocrinol Metab. 2014;99(3):891–7.
41. Boyce AM, Chong WH, Yao J, Gafni RI, Kelly MH, Chamberlain CE, Bassim C, Cherman N, Ellsworth M, Kasa-Vubu JZ, et al. Denosumab treatment for fibrous dysplasia. J Bone Miner Res. 2012;27(7):1462–70.
42. Hernandez M, Phulpin B, Mansuy L, Droz D. Use of new targeted cancer therapies in children: effects on dental development and risk of jaw osteonecrosis: a review. J Oral Pathol Med. 2017;46(5):321–6.
43. Semler O, Netzer C, Hoyer-Kuhn H, Becker J, Eysel P, Schoenau E. First use of the RANKL antibody denosumab in osteogenesis imperfecta type VI. J Musculoskelet Neuronal Interact. 2012;12(3):183–8.
44. Gossai N, Hilgers MV, Polgreen LE, Greengard EG. Critical hypercalcemia following discontinuation of denosumab therapy for metastatic giant cell tumor of bone. Pediatr Blood Cancer. 2015;62(6):1078–80.
45. Roux S, Massicotte MH, Huot Daneault A, Brazeau-Lamontagne L, Dufresne J. Acute hypercalcemia and excessive bone resorption following anti-RANKL withdrawal: case report and brief literature review. Bone. 2019;120:482–6.

Publisher's Note

9 Eigenanteil an den vorgelegten Arbeiten

Der Beitrag des Doktoranden, der in dem Fachartikel „Aneurysmal bone cyst: A review of 65 patients" als Erstautor und in „Aneurysmal bone cyst: results of an off label treatment with Denosumab" als Ko-Autor auftritt, umfasst zum einen die Kontaktaufnahme mit den Patienten, sowie die eigenständige Erhebung und Auswertung der Patientendaten. Zum anderen war er in Zusammenarbeit mit Prof. Dr. H.R. Dürr an der klinischen Interpretation der Daten, sowie an der Verfassung und Überarbeitung beider Veröffentlichungen maßgeblich beteiligt.

10 Literaturverzeichnis

1. Jaffe, H.L. and Lichtenstein L. Solitary unicameral bone cyst: with emphasis on the roentgen picture, the pathology appearance and the pathogenesis. Archives of Surgery, 1942. 44(6): p. 1004-1025.
2. Martinez, V. and H.A. Sissons, Aneurysmal bone cyst. A review of 123 cases including primary lesions and those secondary to other bone pathology. Cancer, 1988. 61(11): p. 2291-304.
3. Vergel De Dios, A.M., et al., Aneurysmal bone cyst. A clinicopathologic study of 238 cases. Cancer, 1992. 69(12): p. 2921-31.
4. Sciot, R., et al., Cytogenetic-morphologic correlations in aneurysmal bone cyst, giant cell tumor of bone and combined lesions. A report from the CHAMP study group. Mod Pathol, 2000. 13(11): p. 1206-10.
5. Pietschmann, M.F., et al., Aneurysmal Bone Cysts of Soft Tissue Represent True Neoplasms: A Report of Two Cases. JBJS, 2011. 93(9): p. e45.
6. Clough, J.R. and C.H.G. Price, Aneurysmal Bone Cyst: Pathogenesis and Long Term Results of Treatment. A Publication of The Association of Bone and Joint Surgeons® | CORR®, 1973. 97: p. 52-63.
7. Kransdorf, M.J. and D.E. Sweet, Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging. American Journal of Roentgenology, 1995. 164(3): p. 573-580.
8. Panoutsakopoulos, G., et al., Recurrent t(16;17)(q22;p13) in aneurysmal bone cysts. Genes Chromosomes Cancer, 1999. 26(3): p. 265-6.
9. Baumhoer, D., F. Amary, and A.M. Flanagan, An update of molecular pathology of bone tumors. Lessons learned from investigating samples by next generation sequencing. Genes Chromosomes Cancer, 2019. 58(2): p. 88-99.
10. Ye, Y., et al., TRE17/USP6 oncogene translocated in aneurysmal bone cyst induces matrix metalloproteinase production via activation of NF-kappaB. Oncogene, 2010. 29(25): p. 3619-29.
11. Lau, A.W., et al., TRE17/ubiquitin-specific protease 6 (USP6) oncogene translocated in aneurysmal bone cyst blocks osteoblastic maturation via an autocrine mechanism involving bone morphogenetic protein dysregulation. J Biol Chem, 2010. 285(47): p. 37111-20.
12. Park, H.Y., et al., Current management of aneurysmal bone cysts. Current Reviews in Musculoskeletal Medicine, 2016. 9(4): p. 435-444.
13. Reddy, K.I.A., et al., Aneurysmal Bone Cysts: Do Simple Treatments Work? Clinical Orthopaedics and Related Research®, 2014. 472(6): p. 1901-1910.

14. Rossi, G., et al., How effective is embolization with N-2-butyl-cyanoacrylate for aneurysmal bone cysts? International Orthopaedics, 2017. 41(8): p. 1685-1692.

15. Terzi, S., et al., Efficacy and Safety of Selective Arterial Embolization in the Treatment of Aneurysmal Bone Cyst of the Mobile Spine: A Retrospective Observational Study. Spine (Phila Pa 1976), 2017. 42(15): p. 1130-1138.

16. Batisse, F., et al., Aneurysmal bone cyst: A 19-case series managed by percutaneous sclerotherapy. Orthop Traumatol Surg Res, 2016. 102(2): p. 213-6.

17. Palmerini, E., et al., Denosumab in patients with aneurysmal bone cysts: A case series with preliminary results. Tumori, 2018. 104(5): p. 344-351.

18. Bekker, P.J., et al., A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. 2004. J Bone Miner Res, 2005. 20(12): p. 2275-82.

19. Thomas, D.M., RANKL, denosumab, and giant cell tumor of bone. Curr Opin Oncol, 2012. 24(4): p. 397-403.

20. Kurucu, N., et al., Denosumab treatment in aneurysmal bone cyst: Evaluation of nine cases. Pediatr Blood Cancer, 2018. 65(4).

21. Lange, T., et al., Denosumab: a potential new and innovative treatment option for aneurysmal bone cysts. Eur Spine J, 2013. 22(6): p. 1417-22.

22. Pauli, C., et al., Response of an aggressive periosteal aneurysmal bone cyst (ABC) of the radius to denosumab therapy. World J Surg Oncol, 2014. 12: p. 17.

23. Dubory, A., et al., Interest of Denosumab for the Treatment of Giant-cells Tumors and Aneurysmal Bone Cysts of the Spine. About Nine Cases. Spine (Phila Pa 1976), 2016. 41(11): p. E654-60.

24. Fontenot, P.B., et al., Recurrent Aneurysmal Bone Cyst of the Distal Fibula Treated with Denosumab and Curettage. Case Rep Oncol Med, 2018. 2018: p. 1574343.

25. Asi, K.W., et al., Massive aneurysmal bone cyst of the skull base treated with denosumab. Head Neck, 2018. 40(12): p. E107-e113.

26. Ghermandi, R., et al., Denosumab: non-surgical treatment option for selective arterial embolization resistant aneurysmal bone cyst of the spine and sacrum. Case report. Eur Rev Med Pharmacol Sci, 2016. 20(17): p. 3692-5.

27. Patel, R.S., et al., Denosumab: a potential treatment option for aneurysmal bone cyst of the atlas. Eur Spine J, 2018. 27(Suppl 3): p. 494-500.

28. Ntalos, D., et al., Therapeutic Management of a Substantial Pelvic Aneurysmatic Bone Cyst Including the Off-Label Use of Denosumab in a 35-Year-Old Female Patient. Case Rep Orthop, 2017. 2017: p. 9125493.

29. Skubitz, K.M., et al., Response of Aneurysmal Bone Cyst to Denosumab. Spine (Phila Pa 1976), 2015. 40(22): p. E1201-4.

30. Pelle, D.W., et al., Targeting receptor-activator of nuclear kappaB ligand in aneurysmal bone cysts: verification of target and therapeutic response. Transl Res, 2014. 164(2): p. 139-48.

31. Thomas, D., et al., Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. Lancet Oncol, 2010. 11(3): p. 275-80.

11 Danksagung

Zuerst möchte ich allen Patienten für ihre großartige Bereitschaft, an dieser Studie teilzunehmen, danken. Ohne Sie wäre dieses Projekt nicht möglich gewesen.

Mein weiterer Dank gilt allen an der Entstehung und Verfassung dieser Arbeit beteiligten Koautoren und Mitarbeitern des Schwerpunkts Tumororthopädie der Klinik für Orthopädie, Physikalische Medizin und Rehabilitation des Klinikums der Ludwig-Maximilians-Universität München.

Außerdem danke ich meinen Kommilitonen, Freunden und meiner Familie, insbesondere meinem Großvater, für die fortwährende Unterstützung und Motivation während der Erstellung dieser Arbeit.

Zuletzt gilt mein größter Dank meinem Doktorvater und Betreuer, Prof. Dr. Hans Roland Dürr, für die konzeptionelle Ausarbeitung und für die tatkräftige Unterstützung in allen Phasen dieses Projektes. Ohne Druck auszuüben, war er zu jeder Zeit und bei jedem Problem für mich erreichbar. Er ist ein großes Vorbild für mich geworden, nicht nur in der wissenschaftlichen Herangehensweise an seine Arbeit, sondern auch in seinem persönlichen Umgang mit Kollegen und Patienten.