



## CASE STUDY AND LITERATURE REVIEW

# Usage of Denosumab for Giant Cell Rich Tumors: A Case Study and Literature Review

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### Abstract

Denosumab is a human monoclonal antibody to receptor activator of NF- $\kappa$ B ligand (RANKL), which has been FDA-approved for the management of giant cell tumor of bone. Here, we present a case of 21-year-old female with solid aneurysmal bone cyst (ABC) treated with denosumab for 6 months to date. The patient experienced positive outcomes as the result of denosumab therapy. Although the use of denosumab has been reported in a number of studies, its off-label use for treatment of ABC and other giant cell rich tumors is not well researched. In addition to a case study, we present a literature review of the off-label use of denosumab for ABCs, central giant cell granuloma, chondroblastoma, osteoblastoma, and fibrous dysplasia.

of bone, the recommended dosage is 120 mg every four weeks with additional 120 mg doses on days 8 and 15 of the first month of therapy, subcutaneous. Patients receiving denosumab treatment are at risk of hypocalcemia, rebound hypercalcemia, osteonecrosis of the jaw, and embryo-fetal toxicity. Therefore, calcium and vitamin D supplements, routine oral exams, and use of contraceptives may be necessary for some patients [4-6].

Off label uses of denosumab have been documented in the literature for other giant cell rich tumors. Here we present a case of using denosumab to treat aneurysmal bone cyst (ABC) and a literature review of the off-label uses of denosumab in other giant cell rich tumors and related bone tumors.

### Introduction

RANK ligand (RANKL) is a transmembrane protein that binds to its receptor, RANK, which is expressed on the surface of osteoclasts, their precursors, and osteoclast-like giant cells. Signaling through RANKL and RANK receptor subsequently leads to osteolysis and tumor growth. Denosumab (Xgeva) is a RANKL inhibitor that binds to RANKL, preventing RANKL-RANK receptor signaling thus stopping osteolysis and tumor growth [1-3]. Denosumab is approved by the United States food and drug administration (FDA) for “prevention of skeletal-related events in patients with bone metastases from solid tumors” and “treatment of adults and skeletally mature adolescents with giant cell tumor of bone that is unresectable or where surgical resection is likely to result in severe morbidity”. For bone metastasis from solid tumors, the recommended dosage is 120 mg every four weeks, subcutaneous. For giant cell tumor

### Case Study

A twenty-one-year-old female presented with one-year of severe shooting pain down her right leg. Magnetic resonance imaging (MRI) of the lumbar spine showed minimal disc bulge at L5-S1 but a partially visualized right hemisacrum mass of 5.2 cm TV  $\times$  3.5 cm AP. Computed tomography (CT) of the abdomen and pelvis showed a 5.8  $\times$  6.6  $\times$  7.3 cm right sacral mass with “cortical breakthrough and bone cysts with fluid levels” and a 6.0 cm right ovarian mature teratoma. Subsequent MRI sacrum showed the right sacral mass with numerous small cystic components with fluid as well as the right ovarian dermoid. Differential diagnoses include sacral chordoma, giant cell tumor, giant cell reparative granuloma (solid aneurysmal bone cyst), chondrosarcoma, chondromalacia of the fibroma,



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benign fibrous histiocytoma. She underwent a CT-guided core biopsy of the sacral mass. Pathology was most consistent with giant cell reparative granuloma (solid ABC). Although surgical resection of sacral giant cell tumors may alleviate the mass effect of the tumors on surrounding vascular and neurological structures, this operative treatment approach may compromise important functions resulting in urinary incontinence or bladder incontinence [7]. We found a review article by Alhumaid 2019 that concluded, "Taking into account the limited existing literature, denosumab therapy appears to offer therapeutic clinical and radiological benefits in select patients with ABCs, particularly those patients with locally advanced, recurrent or inoperable diseases". Therefore, we recommended a neo-adjuvant treatment of denosumab 120 mg subcutaneous injection every 28 days for 6 months followed by surgery. Patient agreed to the treatment plan. Baseline level of calcium was 9.4, phosphate 2.3, magnesium 1.6, and creatinine 1.7. At 6 weeks of follow up, her pain improved and she was tolerating denosumab well. At 11 weeks of follow up, MRI sacrum showed 6.4 × 4.4 × 6.5 cm sacral mass and 6 × 6 cm pelvis mass. At 12 weeks of follow up, she complained of persistent discomfort. At 18 weeks of follow up, she had no bowel, bladder, or sexual dysfunction. At 5 months of follow up, CT abdomen and pelvis scan showed an interval decrease in size to 5.3 cm AP × 6.4 cm TV × 6.5 cm SI and increased sclerosis. The mass demonstrated a persistent but decreased internal cystic/soft tissue component. The right S2-S4 neuroforamina were still obscured by the mass. The mass was still inseparable from the right piriformis muscle. The right ovarian dermoid of 7.3 cm SI remained unchanged in size. At 6 months follow up, the patient was doing well with no new symptoms and her calcium level was 9.4, phosphate was 2.2, magnesium was 1.9, and creatinine was 0.77, and GFR 110. At the most recent visit at 7 month, her latest lab values were calcium 9.1, phosphate 2.5, magnesium 1.8, creatinine 0.77, CFR 110. We recommended the patient to continue with denosumab for another 6 months and monitor her symptoms monthly with a scheduled CT abdomen and pelvis scan at 1 year of denosumab use.

## Discussion

Our case illustrates the successful usage of denosumab in the management of ABC. We expected this outcome given that the literature has reported the effectiveness of denosumab in aneurysmal bone cyst [8]. The patient's clinical improvement and radiographic findings over the six-month course of denosumab treatment prompted us to rethink that perhaps surgery may not be necessary immediately. Therefore, the patient did not undergo surgery as previously planned. Our case highlights that the usage of denosumab allows for avoidance of surgery which is associated with the risk of neurological and vascular injuries. Additionally, our patient did not develop the most common adverse

reactions and side effects with the usage of denosumab.

Our case is another example of the off-label use of denosumab. Here we describe other off-label uses of denosumab in the treatment of other giant cell rich tumors and related bone tumors since the FDA approval of denosumab use for bone metastases from solid tumors and giant cell tumor of bone in 2013.

## Aneurysmal bone cysts

Aneurysmal bone cysts (ABCs) are uncommon, but destructive lesions which frequently present in pediatric patients and young adults [9]. Patients typically present with complaints and evidence of swelling, pain, fractures, and osteolysis [10]. Traditionally, ABCs were believed to develop as the result of a vascular disturbance within the bone which led to increased intraosseous pressure and subsequent development of cyst-like cavities which contain blood. However, new research also supports the role of the TRE17/USP6 oncogene in the pathogenesis of this disease [8,11].

Histologically, these lesions are comprised of cysts filled with blood and fibrous septations comprised of multinucleated giant cells, spindle cells, fibroblasts, and calcifications [9,10,12]. Primary ABCs commonly occur in the spinal column, which presents a multitude of challenges and is associated with increased risk of neurological deficits and morbidity [12,13]. The standard of care for ABCs remains surgical resection and curettage, despite the high morbidity rate [14]. Alternative therapies such as radiotherapy, sclerotherapy, and arterial embolization are used as well [10,14].

Given the histological similarities between ABCs and giant cell rich tumors, denosumab has been used off-label for the treatment of ABCs. However, considering its off-label use, this medication is predominantly used in patients with locally advanced, recurrent, or inoperable disease [8]. A comprehensive review of the use of denosumab in ABCs, conducted in 2019, concluded that denosumab therapy offers considerable therapeutic and radiographic benefits to patients [8]. Another 2019 review suggests that neoadjuvant treatment of giant cell tumors of the bone, such as ABCs, can help to downstage tumors and results in less morbid surgeries, foregoing the need for complete surgical resection [15]. Research published by Grahneis, et al. discussed 65 patients with ABCs, 2 of which were treated with embolization followed by systemic denosumab. The results showed stable disease, requiring no need for further treatment [16]. Further research conducted by Maximen, et al. analyzed the data of 43 patients with ABCs who were treated with denosumab. Alleviation of pain and neurological symptoms was significant as well as radiographic assessment which showed substantial ossification and volume reduction in tumor size [17]. A case published in 2016 reported the successful use of

denosumab in two patients with ABCs of the lumbar spine who were both pain free after 11-13 administrations of denosumab, 120 mg once per week for 4 weeks followed by 120 mg every 40 days, as well as complete ossification of their lesions upon radiographic imaging [12]. In 2018 a case series examined the usage of denosumab in 9 patients with ABCs of the spine and pelvis. Each patient received 120 mg of denosumab on day 1, 8, 15, and 29 followed by an injection every 4 weeks, which resulted in all patients who were symptomatic of their ABCs (8 out of 9 patients) reporting complete resolution of their symptoms. At the end of this study, all patients were free of progressive disease [18].

Furthermore, Raux, et al. reported the complete resolution of pain and reduction of neurological deficits in 5 pediatric patients with inoperable ABCs (4 in the spine), as well as favorable imaging which showed a decrease in lesion size and signs of bone healing [19]. More recently, the 2021 case of a 13-year-old male with a three month history of neck pain and movement restrictions, who was diagnosed with an ABC of the cervical spine, was published. The patient was determined to be resistant to surgery, arterial embolization, and radiotherapy and was subsequently treated with 120 mg of denosumab every 4 weeks, for a total of 6 cycles. The results of this case showed that the patient experienced complete resolution of clinical symptoms by the end of his treatment and his T2 weighted magnetic resonance imaging (MRI) showed evidence of decreased fluid filled levels within his ABC and overall tumor size by his 6<sup>th</sup> cycle of therapy [20].

Of note, a post-mortem study by Hung, et al. in 2022 included two cases of ABCs. Both patients were treated with denosumab for an average of 4.5 months with radiographic evidence of decreased tumor size and increased ossification and mineralization on CT scan. However, when MRI was conducted, the denosumab treated ABCs appeared to have intermediate to hypointense signal and histology showed elongated and curvilinear strands of bone with empty lacunae. The conclusions of this study was that denosumab treated ABCs showed morphologic changes that could mimic other neoplasms. Therefore, treatment and monitoring requires correlation with clinical history and radiographic findings [21].

### Central giant cell granuloma

Central giant cell granulomas (CGCGs) are locally aggressive tumors which most commonly occur in the mandibular region [22]. Histologically, these tumors are similar to giant-cell tumors [23,24]. These tumors are often considerably deforming due to their location and are most commonly treated with surgical curettage [25]. However, this treatment often results in undesirable damage to the jaws, nerves, teeth, and other underlying structures. Plus, recurrence of this disease is often very damaging to the surrounding structures [23,24].

Alternative therapies such as corticosteroids and calcitonin have been suggested, but no clinical trials exists [24,26]. Denosumab therapy as a treatment for this condition is a novel idea, with a majority of published evidence occurring in recent years.

In 2022 the largest study published thus far followed 8 patients diagnosed with CGCG of the jaw over a 75 month period. The average age of these patients was 20.5-years-old and each one was treated with a steadily increasing dosing interval of denosumab. The results showed lesion ossification and size reduction in all patients. However, recurrence occurs in 4 of the 7 patients who completed therapy. Primary lesions were typically larger and more aggressive in those patients with reoccurrence [27]. Mariz, et al. described the case of a 9-year-old girl diagnosed with CGCG and successfully treated denosumab in 2021. The patient underwent corticosteroid therapy, which failed, and was subsequently treated with denosumab and surgery. During her treatment the patient experience osteonecrosis of the jaw, which was promptly treated, as well as several episodes of renal dysfunction and hypercalcemia both during and after denosumab treatment. 2 years following her original diagnosis the patient has not had recurrence of disease or additional episodes of rebound hypercalcemia [28]. Likewise, another recent study, consisting of 6 pediatric patients diagnosed with CGCG was conducted and showed evidence of successful treatment with denosumab. None of the patients showed evidence of recurrence by the end of the study [29]. One month following the publication by Choe, et al., a case series by Pogrel, et al. followed 8 patients, ages 19-32, diagnosed with CGCG over a 60-71-month period. These patients were treated with a regime of denosumab which, by the end of the study, had caused all patient's lesion to become calcified and asymptomatic. No patient had evidence of recurrence over a 5 year period [30].

In the case of familial CGCG, one case study has been conducted, following two sisters with a history of multiple recurrent and aggressive tumors. Both of the patient had undergone previous treatments including surgery and corticosteroid therapy. Eventually, denosumab was delivered as treatment and 3.5 years following their last dose of denosumab, neither patient had evidence of CGCG recurrence [25].

### Chondroblastoma

Chondroblastoma is a relatively rare bone tumor, comprising only 1-2% of all primary bone tumors [31,32]. The histology of the lesion is characterized by chondroblasts and osteoclastic-like giant cells, while the pathology of this malignancy is believed to originate in the osteoclast-like giant cells via the RANK/RANK-L pathway. The current treatment paradigm for chondroblastoma is surgical resection and occasional radiotherapy [33-38].

Due to the role of the RANK/RANK-L pathway in the pathogenesis of chondroblastoma, the first known usage of denosumab as therapy for chondroblastoma was published in 2017. The case described a 64-year-old male, status post two surgical resections, who was found to have recurrence of his chondroblastoma at the right temporal bone. The patient was started on denosumab therapy and at his 1-year follow up there was no evidence of recurrence. However, repeat imaging 2 years after his initial diagnosis showed recurrence of disease and the patient was again started on denosumab. Following his second course of denosumab, the patient did not experience recurrence of disease [39]. The second reported use of denosumab in chondroblastoma involved a 15-year-old male diagnosed with a lesion of his right ischium and inferior pubic ramus. The patient was started on neoadjuvant denosumab to facilitate bone reconstitution due to the belief that the patient's diseased area of bone would not support curettage and bone grafting. The patient was treated over a 12-week period and then underwent resection of his right pubis and ischium. However, recurrence occurred 8 months post-operation and the patient was again treated with denosumab followed by curettage, radiofrequency ablation, and bone grafting. 4 years later, the patient is well without evidence of recurrence [40]. The latest known use of denosumab for chondroblastoma involved a 16-year-old male presenting for left shoulder pain. Imaging confirmed chondroblastoma of the proximal left humerus as well as evidence of metastasis to the lungs, bilaterally. Surgical resection was determined to not be feasible due to the diffuse nature of disease. As a result, denosumab therapy was started and resulted in progressive minimal reduction and calcification of all lung nodules without evidence of new disease. 20 months following initiation of denosumab, the patient had no new calcifications in the lungs or left humerus as well as decreased size of all pre-existing nodules [41].

## Osteoblastoma

Osteoblastomas are an uncommon class of bone malignancy with a little understood pathogenesis. Current research points towards chromosomal abnormalities and alteration in transcription factors as the main molecular pathologies which lead to their development [42,43]. Clinical symptoms of osteoblastoma are similar to other bone tumors and include pain, pathologic fractures, and localized swelling. These lesions are often difficult to differentiate from other bone tumors due to their indistinct and localized nature on plain radiography. But some have been known to grow extensively and into the intracortical region of bones. Thus, easily becoming confused with an ABC [44]. Nonetheless, research has shown that osteoblastomas consist predominantly of osteoblasts. These cells exhibit high levels of the RANKL, which leads to high levels of osteoclastic activity and bone resorption. Therefore, by inhibiting the RANK-RANKL pathway, osteoclastic activity could be reduced

and the deleterious effects of osteoblasts could be reduced as well [45,46].

As a result of its mechanism of action, denosumab has been used as therapy in patients with known osteoblastoma. Published by Reynold, et al., in 2014, the case of a 14-year-old male with an osteoblastoma of the sacrum discussed the use of neo-adjuvant denosumab following en bloc resection. The patient proved to be resistant to radiofrequency ablation and therefore denosumab therapy was administered which resulted in MRI changes indicating osteosclerosis. Post-operative histological findings showed the absence of osteoclasts within and around a sclerotic lesion. Overall, the use of denosumab in this 14-year-old patient caused tumor regression and conversion into a sclerotic mass with well-defined margins. However, it is important to note that in this case, denosumab therapy did not stop the metabolic activity of the lesion, which is why en bloc resection was still pursued [47]. A 2019 case describes the use of denosumab in an 18-year-old male with a history of pain and swelling in his right thumb. Biopsy of this patient's lesion confirmed osteoblastoma and the patient decided on a trial of denosumab therapy. Following this treatment, the patient experienced no pain and had full range of motion of his right thumb. Two years later, the patient experienced recurrence of disease and was again treated with denosumab, which reduced his pain and allow for full range of motion [48]. Lastly, Wong, et al. reported the case of a 20-year-old female who presented with evidence of an osteolytic lesion in her left lateral sacrum. The patient was eventually diagnosed with an osteoblastoma with secondary ABCs. However, due to the location, surgical resection was determined to be too morbid and the patient was treated with denosumab. This therapy stabilized and decreased the size of her lesion as well as pain, allowing her to no longer require pain management therapy [49].

## Fibrous dysplasia

Fibrous dysplasia (FD) is a rare genetic disorder, in which the normal bone and bone marrow are replaced with abnormal fibrous and immature osseous tissue. Patients with FD often present with skeletal pain, deformities, and a history multiple fractures [50]. This disease can be accompanied by hyper functioning endocrinopathies such as McCune-Albright syndrome, which is caused by a mutation of the GNAS gene. This gene mutation alters downstream cascades of the Gs-coupled protein receptor and leads to increased levels of RANKL, causing an overexpression of osteoclastic activities [51]. The current treatment paradigm includes surgical intervention to mediate fractures and deformities in addition to medical therapy using bisphosphonates, which have been shown to be ineffective in the treatment of severe FD [50,51]. Therefore, off-label use of denosumab has been suggested as an alternative treatment [50,51].



A case report by Boyce, et al. involved a 9-year-old boy with severe FD suffering from an aggressive femoral lesion. High-dose denosumab was administered and induced remarkable reduction in pain, bone turnover markers (BTMs), and tumor growth rate. However, discontinuation of denosumab led to dramatic bone turnover rebound and severe hypercalcemia [50]. Later case reports with low-dose denosumab in adult patients also showed efficacy in pain relief and BTMs reductions [51-54]. Adjusted dosage (escalated or tampered) throughout the treatment may be required depending on the patient and clinical scenario [52,54,55]. Meier, et al. conducted an observational study by following 37 adult patients who were diagnosed with FD and treated with denosumab. 21 of these patients experienced improvements in pain and BTMs whereas 16 patients discontinued denosumab due to insufficient pain relief or severe side effects [55]. Continued post-treatment follow-up with a median of 3.2 years revealed BTM rebound that exceeded pretreatment levels. It was determined that high rebound BTMs was associated with high pretreatment levels, good response to denosumab, and multiple injections. Otherwise, no other lesion progressions, fractures, or pain flares were observed and only one patient was found to have asymptomatic hypercalcemia [55]. Although denosumab for the treatment of adult FD patients seem to provide promising outcomes with minimal side effects, withdrawal safety raises concerns and further studies are warranted.

## Conclusion

The effectiveness of denosumab varies depending on the pathology of the patient and clinical scenario. Patients with ABCs, CGCGs, osteoblastoma, fibrous dysplasia, and chondroblastoma may all benefit from denosumab therapy, especially disease processes which have been shown to be advanced, metastatic, recurrent, or inoperative. However, the potential adverse effects of initiating denosumab therapy, such as hypercalcemia, osteonecrosis, and recurrence of primary disease following cessation of therapy, must all be considered. Overall, further clinical trials are necessary to determine denosumab's precise place in therapeutic management of giant cell rich bone tumors and other osteolytic diseases.

## Disclosure of Conflicts of Interest

No conflicts of interest exist for any of the authors.

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## References

- Hanley DA, Adachi JD, Bell A, Brown V (2012) Denosumab: Mechanism of action and clinical outcomes. *Int J Clin Pract* 66: 1139-1146.
- (2013) United states food and drug administration: Xgeva (denosumab) Label.
- Palmerini E, Picci P, Reichardt P, Downey G (2019) Malignancy in giant cell tumor of bone: A review of the literature. *Technol Cancer Res Treat* 18.
- Pittman K, Antill YC, Goldrick A, Goh J, de Boer RH (2017) Denosumab: Prevention and management of hypocalcemia, osteonecrosis of the jaw and atypical fractures. *Asia Pac J Clin Oncol* 13: 266-276.
- Chapurlat R (2018) Effects and management of denosumab discontinuation. *Jt bone spine* 85: 515-517.
- Lamy O, Stoll D, Aubry-Rozier B, Rodriguez EG (2019) Stopping denosumab. *Curr Osteoporos Rep* 17: 8-15.
- Thangaraj R, Grimer RJ, Carter SR, Stirling AJ, Spilsbury J, et al. (2010) Giant cell tumour of the sacrum: A suggested algorithm for treatment. *Eur Spine J* 19: 1189-1194.
- Alhumaid I, Abu-Zaid A (2019) Denosumab therapy in the management of aneurysmal bone cysts: A comprehensive literature review. *Cureus* 11: e3989.
- Rapp TB, Ward JP, Alaia MJ (2012) Aneurysmal bone cyst. *J Am Acad Orthop Surg* 20: 233-241.
- Tsagozis P, Brosjo O (2015) Current strategies for the treatment of aneurysmal bone cysts. *Orthop Rev (Pavia)* 7.
- Ye Y, Pringle LM, Lau AW, Riquelme DN, Wang H, et al. (2010) TRE17/USP6 oncogene translocated in aneurysmal bone cyst induces matrix metalloproteinase production via activation of NF-kappaB. *Oncogene* 29: 3619-3629.
- Ghermandi R, Terzi S, Gasbarrini A, Boriani S (2016) 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* 20: 3692-3695.
- Lim JBT, Sharma H, Reid R, Reece AT (2012) Aneurysmal bone cysts of the vertebrae. *J Orthop Surg (Hong Kong)* 20: 201-204.
- Park HY, Yang SK, Sheppard WL, Hegde V, Zoller SD, et al. (2016) Current management of aneurysmal bone cysts. *Curr Rev Musculoskelet Med* 9: 435-444.
- Lipplaa A, Dijkstra S, Gelderblom H (2019) Challenges of denosumab in giant cell tumor of bone, and other giant cell-rich tumors of bone. *Curr Opin Oncol* 31: 329-335.
- Grahneis F, Klein A, Baur-Melnyk A, Knosel T, Birkenmaier C, et al. (2019) Aneurysmal bone cyst: A review of 65 patients. *J bone Oncol* 18: 100255.
- Maximen J, Robin F, Tronchot A, Rossetti A, Ropars M, et al. (2022) Denosumab in the management of aneurysmal bone cyst. *Jt bone spine* 89: 105260.
- Palmerini E, Ruggieri P, Angelini A, Boriani S, Campanacci D, et al. (2018) Denosumab in patients with aneurysmal bone cysts: A case series with preliminary results. *Tumori* 104: 344-351.
- Raux S, Bouhamama A, Gaspar N, Brugieres L, Entz-Werle N, et al. (2019) Denosumab for treating aneurysmal bone cysts in children. *Orthop Traumatol Surg Res* 105: 1181-1185.
- Fadavi P, Arefpour AM, Hariri R, Vasheghani M, Garousi M, et al. (2021) Dramatic response of aneurysmal bone cyst to denosumab: Case report and literature review. *Clin Case Rep* 9: e04993.
- Hung YP, Bredella MA, Lobmaier IVK, Lozano-Calderon

- SA, Rosenberg AE, et al. (2022) Aneurysmal bone cyst and osteoblastoma after neoadjuvant denosumab: Histologic spectrum and potential diagnostic pitfalls. *APMIS* 130: 206-214.
22. Cloutier M, Charles M, Carmichael RP, Sandor GKB (2007) An analysis of peripheral giant cell granuloma associated with dental implant treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 103: 618-622.
  23. Pogrel AM (2012) The diagnosis and management of giant cell lesions of the jaws. *Ann Maxillofac Surg* 2: 102-106.
  24. de Lange J, van den Akker HP, van den Berg H (2007) Central giant cell granuloma of the jaw: A review of the literature with emphasis on therapy options. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 104: 603-615.
  25. Ryttonen E, Ottavainen V, Ryttonen A, Uusitalo S, Lehenkari P, et al. (2018) Denosumab treatment for aggressive multiple recurrent familial central giant-cell granulomas. *Ann Maxillofac Surg* 8: 265-269.
  26. Harris M (1993) Central giant cell granulomas of the jaws regress with calcitonin therapy. *Br J Oral Maxillofac Surg* 31: 89-94.
  27. Rhou YJJ, Wang C-J, Nguyen M, Vanderniet JA, Munns CF, et al. (2022) Clinical and radiologic response of central giant cell granuloma to denosumab: A 6-year prospective observational study. *Calcif Tissue Int* 110: 464-474.
  28. Mariz BALA, Migliorati CA, Alves F de A, Penteado F de M, Carvalho NP, et al. (2021) Successful denosumab treatment for central giant cell granuloma in a 9-year-old child. *Spec Care Dentist* 41: 519-525.
  29. Choe M, Smith V, Okcu MF, Wulff J, Gruner S, et al. (2021) Treatment of central giant cell granuloma in children with denosumab. *Pediatr Blood Cancer*.
  30. Pogrel MA, Hossaini-Zadeh M (2021) Denosumab for the management of central giant cell granuloma of the jaws-a case series. *Int J Oral Maxillofac Surg* 50: 1019-1022.
  31. Schajowicz F, Gallardo H (1970) Epiphysial chondroblastoma of bone. A clinico-pathological study of sixty-nine cases. *J Bone Joint Surg Br* 52: 205-226.
  32. Dahlin DC, Ivins JC (1972) Benign chondroblastoma. A study of 125 cases. *Cancer* 30: 401-413.
  33. Thomas DM, Skubitz KM (2009) Giant cell tumour of bone. *Curr Opin Oncol* 21: 338-344.
  34. Zheng MH, Robbins P, Xu J, Huang L, Wood DJ, et al. (2001) The histogenesis of giant cell tumour of bone: A model of interaction between neoplastic cells and osteoclasts. *Histol Histopathol* 16: 297-307.
  35. McCarthy EF, Frassica FJ (2014) Pathology of bone and joint disorders. Cambridge University Press.
  36. Ramappa AJ, Lee FY, Tang P, Carlson JR, Gebhardt MC, et al. (2000) Chondroblastoma of bone. *J Bone Joint Surg Am* 82: 1140-1145.
  37. Springfield DS, Capanna R, Gherlinzoni F, Picci P, Campanacci M (1985) Chondroblastoma. A review of seventy cases. *J Bone Joint Surg Am* 67: 748-755.
  38. Suneja R, Grimer RJ, Belthur M, Jeys L, Carter SR, et al. (2005) Chondroblastoma of bone: Long-term results and functional outcome after intralesional curettage. *J Bone Joint Surg Br* 87: 974-978.
  39. Calvert N, Wood D (2017) Use of denosumab in recurrent chondroblastoma of the squamous temporal bone: A case report. *Clin case reports* 5: 411-413.
  40. Visgauss JD, Lazarides A, Dickson B, Cardona D, Sheth M, et al. (2021) Treatment of chondroblastoma with denosumab: A case report with a correlative analysis of effect on the rank signaling pathway. *JBJS Case Connect* 11.
  41. Focaccia M, Gambarotti M, Hakim R, Paioli A, Cesari M, et al. (2021) Chondroblastoma's lung metastases treated with denosumab in pediatric patient. *Cancer Res Treat* 53: 279-282.
  42. Fittall MW, Mifsud W, Pillay N, Ye H, Strobl A-C, et al. (2018) Recurrent rearrangements of FOS and FOSB define osteoblastoma. *Nat Commun* 9: 2150.
  43. Nord KH, Nilsson J, Arbajian E, Vult von Steyern F, Brosjo O, et al. (2013) Recurrent chromosome 22 deletions in osteoblastoma affect inhibitors of the Wnt/beta-catenin signaling pathway. *PLoS One* 8: e80725.
  44. Greenspan A (1993) Benign bone-forming lesions: Osteoma, osteoid osteoma, and osteoblastoma. Clinical, imaging, pathologic, and differential considerations. *Skeletal Radiol* 22: 485-500.
  45. Atkins GJ, Kostakis P, Pan B, Farrugia A, Gronthos S, et al. (2003) RANKL expression is related to the differentiation state of human osteoblasts. *J Bone Miner Res* 18: 1088-1098.
  46. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, et al. (2010) Denosumab in patients with giant-cell tumour of bone: An open-label, phase 2 study. *Lancet Oncol* 11: 275-280.
  47. Reynolds JJ, Rothenfluh DA, Athanasou N, Wilson S, Kieser DC (2018) Neoadjuvant denosumab for the treatment of a sacral osteoblastoma. *Eur Spine J* 27: 446-452.
  48. Kooner P, Ferguson P (2019) The use of denosumab in osteoblastoma of the metacarpal. *J Hand Surg Am* 44: 994. e1-994.e6.
  49. Wong K, Chantharasamee J, Nelson S, Eckardt MA, Motamedi K, et al. (2021) Aggressive osteoblastoma with a secondary aneurysmal bone cyst treated with denosumab. *Rare Tumors* 13.
  50. Boyce AM, Chong WH, Yao J, Gafni RI, Kelly MH, et al. (2012) Denosumab treatment for fibrous dysplasia. *J Bone Miner Res* 27: 1462-1470.
  51. Meier ME, van der Bruggen W, van de Sande MAJ, Appelman-Dijkstra NM (2021) Regression of fibrous dysplasia in response to denosumab therapy: A report of two cases. *Bone Reports* 14: 101058.
  52. Ganda K, Seibel MJ (2014) Rapid biochemical response to denosumab in fibrous dysplasia of bone: Report of two cases. *Osteoporos Int* 25: 777-782.
  53. Ikuta K, Sakai T, Koike H, Ito K, Imagama S, et al. (2021) Successful treatment with denosumab for pelvic fibrous dysplasia: A case report and review of the literature. *Medicine (Baltimore)* 100: e28138.
  54. Gautam KP, Rajan R, Cherian KE, Kapoor N, Hephzibah J, et al. (2020) A case of recalcitrant fibrous dysplasia treated with denosumab. *Jt Bone Spine* 87: 369-370.
  55. Meier ME, Clercx SN, Winter EM, Pereira AM, van de Ven AC, et al. (2021) Safety of therapy with and withdrawal from denosumab in fibrous dysplasia and McCune-Albright syndrome: An observational study. *J Bone Miner Res* 36: 1729-1738.