Annals of Clinical Case Reports

Case Report
Published: 16 Jan, 2024

Dramatic Response to Denosumab in a Locally Advanced Osteoblastoma of the C5-C6 Vertebrae. A Case Report

Machak GN, Snetkov AI and Romanova TN*

Federal State Budgetary Institution, "National Medical Research Center for Traumatology and Orthopedics named after N.N. Priorov" of the Ministry of Health of the Russian Federation, Russia

Abstract

Osteoblastoma is a rare (1% of all primary bone tumors), benign, locally aggressive bone-forming tumor, commonly observed in the second and third decades of life. There are no established pharmacological options for patients in whom resection is not feasible. Novel pathogenetic therapies are currently being investigated in primary osteolytic bone tumors. We report a case of locally advanced osteoblastoma of the C5-C6 vertebrae treated with denosumab. The tumor response was dramatic and consisted of rapid pain relief, increased cervical spine stability, and significant tumor calcification on CT scan. PET/CT showed a complete metabolic response. Our findings demonstrate the possible involvement of the RANKL-RANK axis in the pathogenesis of osteoblastoma. It has been hypothesized that RANKL inhibition disrupts the vicious cycle at the osteoblastoma microenvironment, leading to tumor ossification and demarcation. Emerging pathogenetic therapy of osteoblastomas can have a significant clinical impact in locally advanced and inoperable cases as neoadjuvant or definitive treatment. Additional experimental and clinical studies are required to confirm the viability of this concept.

Keywords: Osteoblastoma; Spine; RANKL; Vicious cycle; Denosumab

Introduction

Osteoblastoma is a rare (1% of all primary bone tumors), benign, locally aggressive bone-forming tumor, commonly observed in the second and third decades of life [1]. Posterior elements of the spine and the long tubular bones are the most common sites of involvement.

Histologically, osteoblastomas are characterized by interanastomosing trabeculae of woven bone, set within loose edematous fibrovascular stroma [2]. A single layer of polygonal osteoblasts usually rims the bone trabeculae [3]. Osteoblastomas may show different levels of mineralization, from lace-lake osteoid to densely mineralized woven bone that shows multiple cement lines [2]. Osteoclast - like giant cells are scattered throughout the tumor.

The pathogenesis of osteoblastoma is not well understood. Recurrent rearrangements of FOS and its paralogue, FOSB, are thought to be responsible for the loss of the C-terminal end of the FOS protein, rendering it resistant to degradation, causing high expression within tumor cells [4-6]. Truncated FOS protein induces activation of the transcription factor complex AP-1, which drives tumor cells proliferation and aberrant bone remodeling.

In patients with advanced stages, spinal osteoblastomas can compromise the stability of axial skeleton, cause severe neurological dysfunction and may easily recur after surgery. Intralesional curettage or En-bloc resection remains the mainstay treatment. Adequate surgical margins are achieved in approximately half of operated patients with spine tumors [7]. Local control depends on the type of surgery and stage of the disease. The highest recurrence rate was reported after intralesional curettage (23% to 100%), whereas it was below 20% after En-bloc resection [1,8]. In Enneking stage III spinal osteoblastomas, the rate of local relapses after curettage ranged from 50% to 67% [9,10]. Locally advanced primary or recurrent lesions cannot always be controlled surgically due to increased morbidity, so new treatment options are needed in such cases.

Denosumab, a humanized specific monoclonal antibody for the Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL), inhibits osteoclast-mediated bone destruction and is used in the treatment of osteoporosis and osteolytic bone tumors. Experience with RANKL inhibition in osteoblastoma is limited to a few case reports and case series. Off-label use of denosumab has been reported as definitive treatment in cases not amendable for surgery [11-13] or in the neoadjuvant

OPEN ACCESS

Correspondence:
Gennady Machak, Federal State Budgetary Institution, "National Medical Research Center for Traumatology and Orthopedics named after N.N. Priorov" of the Ministry of Health of the Russian Federation, Priorov Street, 10, CITO, Moscow, Russia

Received Date: *21 Dec 2023*
Accepted Date: *11 Jan 2024*
Published Date: *16 Jan 2024*

Citation:
Machak GN, Snetkov AI, Romanova TN. Dramatic Response to Denosumab in a Locally Advanced Osteoblastoma of the C5-C6 Vertebrae. A Case Report. Ann Clin Case Rep. 2024; 9: 2559.
ISSN: 2474-1655.

setting [14-15]. Here, we report the response of locally advanced C5-C6 spine osteoblastoma with the goal to discuss the possible impact of RANKL inhibition on disease pathogenesis and to describe the clinical and imaging evolution following Denosumab therapy.

Case Presentation

An 18-year-old male presented with an approximately 4-years history of cervical pain. The pain intensified with neck movements and required occasional use of pain medications. His neurological examination did not reveal any significant symptoms of nerve roots or spinal cord compression, including varying degrees of sensory or motor impairment. Initial CT scans showed a destructive, osteolytic, expansile lesion involving the vertebral bodies and posterior elements of C5-C6 vertebrae (Figure 1). MRI imaging revealed a heterogeneously enhancing tumor with intermediate signal on both T1 and T2 sequences with a significant soft tissue component that was measured at 55 mm × 55 mm × 37 mm (Figure 2). Tumor growth within spinal canal, in the close proximity of spinal cord but without secondary myelopathy. On several sections, almost the entire left vertebral artery was surrounded by tumor.

An open biopsy performed in March 2023 yielded a diagnosis of an osteoblastoma. Histology showed typical features of an osteoblastoma with disorganized, partly mineralized osteoid and trabeculae of woven bone lined by plump epithelioid osteoblasts. There were numerous scattered osteoclasts on the surface of immature bone. There was no marked nuclear pleomorphism or mitotic activity.

Given the extent of the tumor, which involved two vertebral bodies, posterior elements and left vertebral artery with a large soft tissue component, adequate surgery was deemed to be too morbid. As the lesion contained osteoclasts and was largely lytic, a trial of Denosumab therapy was undertaken in an attempt to reduce and solidify the tumor mass. After obtaining the patient`s consent for the experimental use of Denosumab, we initiated the therapy in accordance with the published approach to Giant Cell Tumors of Bone (GCTB) described by Thomas et al. [16]. The patient started the treatment in a dose 120 mg subcutaneously every week for 4 weeks, and then monthly with oral vitamin D, and calcium supplementation. Seven doses of Denosumab were administered from June 2023 to September 2023 without significant adverse events. His pain control improved significantly and he was able to be completely off all pain medications within 3 months of starting Denosumab. The response also included dramatic tumor calcification on CT scans and increased cervical spine stability (Figure 3). In November 2023, two months after the last dose of Denosumab, PET/CT showed dense sclerosis throughout the previously lytic lesion along with normal FDG avidity, indicating a complete metabolic response. In addition to monitoring the patient every 3 months, maintenance antiresorptive therapy will be discussed in the near future. At the time of writing this report, surveillance imaging showed a stable clinical, neurologic and radiographic appearance.

Discussion

Treatment options for locally advanced or unresectable osteoblastomas of the axial skeleton are limited. The use of radiofrequency ablation, radiotherapy and chemotherapy is still controversial. Therefore, new treatment approaches are required for these patients. The pathogenetic treatment of osteoblastoma discussed here may have significant implications in various clinical situations. Denosumab therapy leads to the disappearance of osteoclast-like giant cells and the rapid conversion of a lytic tumor into a sclerotic tumor due to significant mineralization of woven bone trabeculae. Lesions arising in critical sites such as the spine or head and neck can pose surgical challenges, so neoadjuvant Denosumab may reduce the morbidity of surgical resection and improve functional outcome [14,15]. The same concept is now generally accepted in the treatment of GCTB [17].

The role of Denosumab as the only treatment in patients with osteoblastoma not amendable for surgery is unclear. To our best knowledge, only three case report studies describing this approach have been published [11-13]. Kooner et al. treated an 18-year-old man with osteoblastoma of the first metacarpal bone with six doses of Denosumab during 3 months [11]. Twenty-two months after drug discontinuation, the tumor regrowth was observed on CT and MRI. The same 3 months Denosumab regimen was applied as re-challenge treatment, which again resulted in extensive tumor ossification. After 18 months of follow-up after the last dose of Denosumab, the patient has not progressed.

Wong et al reported a 20-year-old female with an aggressive osteoblastoma and secondary ABCs located in the sacrum [12]. At the time of writing their report, the patient has received 24 doses of Denosumab according to GCTB schedule. Surveillance imaging throughout her treatment showed a decrease in the number and size of the cystic components, and an overall plain radiographic appearance of mineralization along with decreased FDG avidity on PET scan, suggestive of a treatment response.

Yamaga et al. reported a case of unresectable osteoblastoma of the axis controlled with Denosumab in a 17-year-old Japanese woman [13].

Regarding our patient, it was assumed that the planned adequate surgery would be associated with a high risk of complications and local recurrence. A similar clinical situation was reported by Wu et

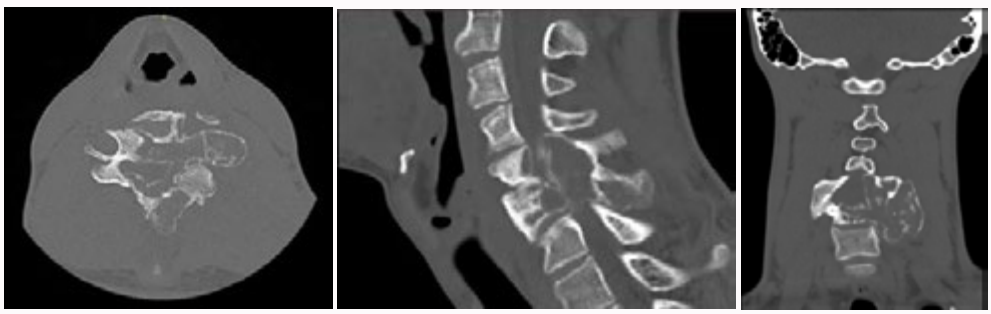

Figure 1: Osteoblastoma of C5-C6 vertebrae. Non-contrast cervical CT scan in bone window before treatment.

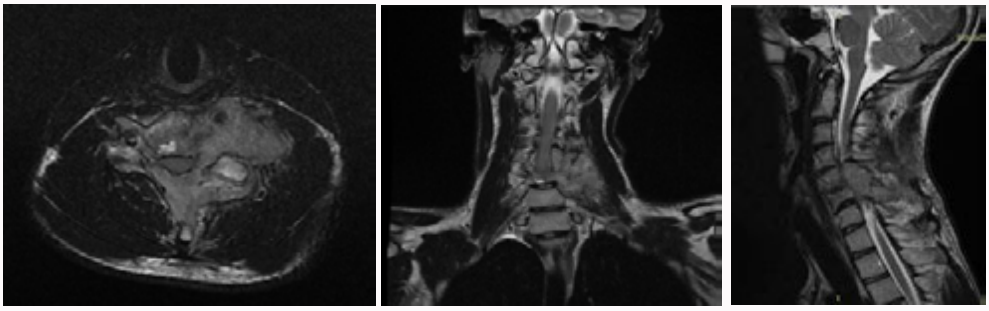

Figure 2: Osteoblastoma of the C5-C6 vertebrae. T2 MRI before treatment.

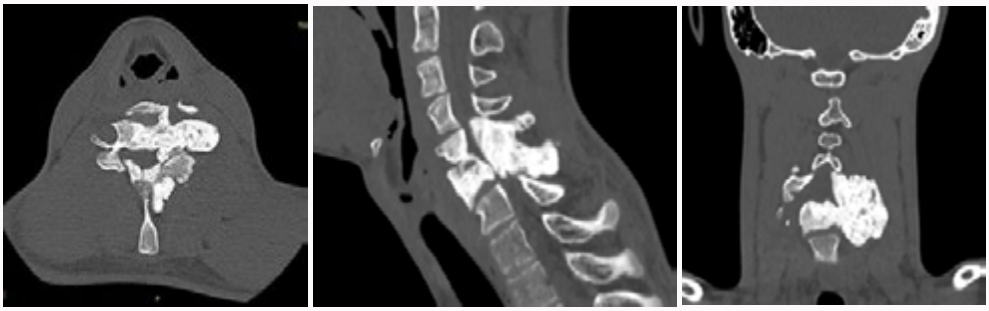

Figure 3: Osteoblastoma of C5-C6 vertebrae. Non-contrast cervical CT scan in bone window after 7 doses of Denosumab.

al. who treated a patient with osteoblastoma involving the C7 and Th1 vertebral bodies [18]. Surgical treatment consisted of anterior hemi–vertebrectomy, spinal decompression combined with titanium mesh, autograft fusion and titanium plate internal fixation from C6 to Th2. In that case, superficial infection and local recurrence occurred, requiring additional surgery and postoperative radiotherapy.

In our case, the initial treatment with Denosumab was aimed at improving the local situation. This resulted in rapid transformation of a locally destructive spinal tumor into an ossified, painless mass, restoring function and avoiding immediate and traumatic surgery. Pronounced ossification of the tumor, a complete metabolic response and planned maintenance therapy allow us to hope for a long progression-free period, which will delay surgery as much as possible, and may even avoid it.

The impressive responses to RANKL inhibition prompted us to revise the pathogenesis of osteoblastoma. It is known that chromosomal rearrangements in this tumor lead to the accumulation of truncated FOS protein in the nucleus [4]. Subsequent up-regulation of the transcription factor complex AP-1 affects the promoter and enhancer regions of a number of genes that regulate a variety of biological processes, including proliferation, differentiation and secretory activity of immature osteoblasts [19,20]. An analogous mechanism was described in another osteolytic tumor, aneurismal bone cyst, where activation of the AP-1 complex occurred because of c-Jun protein stabilization [21].

Given the significant ossification of tumor after Denosumab in our patient, it can be assumed that RANKL-RANK axis is active in this lesion. To confirm this hypothesis, the following facts can be mentioned. First, osteoblastomas are composed primarily of immature and metabolically active bone-forming cells [3,22]. Compared to mature osteoblasts, these cells express higher levels of RANKL mRNA and protein, favoring osteoclastogenesis and bone resorption [23-25]. After osteoblast maturation, expression of RANKL protein decreases 5-fold [24]. Second, osteoclast-like multinucleated giant cells are invariably present in abundance because osteoblastoma undergoes continuous remodeling [2,3]. Third, treatment-induced elimination of giant cells from the Tumor Microenvironment (TME) is followed by a decrease in tumor cell proliferation and metabolic activity observed on PET-CT, both in our case and in other cases [12]. The abundant mineralization of previously formed woven bone may be due to the switch of mutated osteoblastoma cells to a more differentiated phenotype, shifting bone turnover toward re-ossification.

Based on above-mentioned, we hypothesize that a vicious cycle is established at the TME level in osteoblastoma. Immature mutated cells support osteoclastogenesis and ongoing abnormal bone remodeling. It is still unclear whether this block of differentiation is due to intrinsic, extrinsic, or both mechanisms. In turn, osteoclast-like multinucleated giant cells probably inhibit, through paracrine signals, the differentiation of mutated cells and maintain them in a proliferative state with RANKL secretion and, usually, impaired osteoid matrix mineralization. A similar oncogenic mechanism has been found in GCTB [26,27]. This anticipated vicious cycle in osteoblastoma need to be characterized experimentally. The significant imaging and pathological responses in GCTB together with the findings described here support the concept that similarities may exist in the pathogenesis and treatment approaches of these osteolytic lesions.

Some preliminary conclusions can be drawn from a very limited clinical experience with Denosumab in unresectable osteoblastomas. Although RANKL inhibition often eliminates the RANK-positive cell population, it has been suggested that neoplastic cells may survive and reactivate long after drug withdrawal [11]. Despite a presumable differentiation shift, neoplastic cells may maintain their metabolic activity after Denosumab treatment [15]. Unlike GCTB, where

multinucleated giant cells are responsible for increased FDG uptake [28], this role can also be attributed to mutated cells in osteoblastoma. Residual metabolic activity after Denosumab therapy can be visualized on PET-CT, even the tumor is ossified [15]. In our case, a complete metabolic response was observed, but it is unclear how long this response will last after drug discontinuation.

Thus, the tumor response to RANKL inhibition appears to be reversible, and lesion reactivation cannot be ruled out after Denosumab cessation, even after a prolonged progression-free interval. Therefore, for unresectable and clinically aggressive osteoblastomas, at least four scenarios should be considered: 1) reassessment of tumor resectability after initial Denosumab therapy; 2) long-term continuous use of Denosumab in order to maintain constant the TME parameters; 3) drug holidays with close monitoring and early re-challenge with Denosumab in case of relapse; 4) attempts to suppress the viability or stimulate apoptosis of mutated neoplastic cells.

In the context of the further development of conservative approaches to the treatment of selected patients with osteoblastoma, several unanswered questions need to be addressed:

1) What transcriptional changes does denosumab induces in mutated osteoblastoma cells?

2) How long does the anticipated shift in tumor cells differentiation last after Denosumab withdrawal and what are the factors, which return them to a less differentiated, RANKL-expressing, phenotype?

3) What are the current and future modalities to target the neoplastic cell population?

4) What is the optimal duration of Denosumab administration and how safe are drug holidays?

5) Which treatment approach is most appropriate in terms of toxicity, quality of life and costs?

Conclusion

Inhibition of RANKL-RANK axis in osteoblastoma is a pathogenetic treatment with expectedly strong but probably reversible clinical impact. Denosumab therapy may cause elimination of multinucleated giant cells and induce a significant tumor ossification. Preoperative treatment may contribute to the conversion of a locally aggressive tumor into a sclerotic, well-defined lesion with distinct margins, facilitating the function-sparring surgery. In unresectable osteoblastoma, the role and optimal sequencing of Denosumab as definitive therapy remains to be determined. Additional experimental and clinical studies are required to determine the role of pathogenetic interventions in the modern treatment paradigm of osteoblastoma.

References

1. Berry M, Mankin H, Gebhardt M, Rosenberg A, Hornicek F. Osteoblastoma: A 30-year study of 99 cases. J Surg Oncol. 2008;98(3):179-83.
2. Lucas DR. Osteoblastoma. Arch Pathol Lab Med. 2010;134(10):1460-6.
3. Amary F, Bredella MA, Horvai AE, Mahar AM. Osteoblastoma. In: The WHO classification of tumors Editorial Board: WHO classification - Soft Tissue and Bone Tumors, 5th Ed. Lyon: IARC Press; 2020. p. 397-9.
4. Cordier F, Creytens D. New kids on the block: *FOS* and *FOSB* gene. J Clin Pathol. 2023;76(11):721-6.
5. Fittall MW, Mifsud W, Pillay N, Ye H, Strobl AC, Verfaillie A, et al. Recurrent rearrangements of FOS and FOSB define osteoblastoma. Nat Commun. 2018;9(1):2150.
6. van IJzendoorn DGP, Forghany Z, Liebelt F, Vertegaal AC, Jochemsen AG, Bovée JVMG, et al. Functional analyses of a human vascular tumor FOS variant identify a novel degradation mechanism and a link to tumorigenesis. J Biol Chem. 2017;292(52):21282-90.
7. Versteeg AL, Dea N, Boriani S, Varga PP, Luzzati A, Fehlings MG, et al. Surgical management of spinal osteoblastomas. J Neurosurg Spine. 2017;27(3):321-7.
8. Tonai M, Campbell CJ, Ahn GH, Schiller AL, Mankin HJ. Osteoblastoma: Classification and report of 16 patients. Clin Orthop Relat Res. 1982;(167):222-35.
9. Boriani S, Amendola L, Bandiera S, Simoes CE, Alberghini M, Di Fiore M, et al. Staging and treatment of osteoblastoma in the mobile spine: A review of 51 cases. Eur Spine J. 2012;21(10):2003-10.
10. Cao S, Chen K, Jiang L, Wei F, Liu X, Liu Z. Intralesional marginal resection for osteoblastoma in the mobile spine: Experience from a single center. Front Surg. 2022;9:838235.
11. Kooner P, Ferguson P. The use of denosumab in osteoblastoma of the metacarpal. J Hand Surg Am. 2019;44(11):994.e1-994.e6.
12. Wong K, Chantharasamee J, Nelson S, Eckardt MA, Motamedi K, Hornicek FJ, et al. Aggressive osteoblastoma with a secondary aneurysmal bone cyst treated with denosumab. Rare Tumors. 2021;13:20363613211034710.
13. Yamaga K, Kuwamoto S, Tanishima S, Yamashita H, Asano N, Matsushita M, et al. An unresectable osteoblastoma of the axis controlled with denosumab. J Orthop Sci. 2024;29(1):379-83.
14. Hung YP, Bredella MA, Lobmaier IVK, Lozano-Calderón SA, Rosenberg AE, Nielsen GP. Aneurysmal bone cyst and osteoblastoma after neoadjuvant denosumab: Histologic spectrum and potential diagnostic pitfalls. APMIS. 2022;130(4):206-14.
15. Reynolds JJ, Rothenfluh DA, Athanasou N, Wilson S, Kieser DC. Neoadjuvant denosumab for the treatment of a sacral osteoblastoma. Eur Spine J. 2018;27(Suppl 3):446-52.
16. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, et al. Denosumab in patients with giant-cell tumour of bone: An open-label, phase 2 study. Lancet Oncol. 2010;11(3):275-80.
17. Rutkowski P, Ferrari S, Grimer RJ, Stalley PD, Dijkstra SP, Pienkowski A, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. Ann Surg Oncol. 2015;22(9):2860-8.
18. Wu M, Xu K, Xie Y, Yan F, Deng Z, Lei J, et al. Diagnostic and management options of osteoblastoma in the spine. Med Sci Monit. 2019;25:1362-72.
19. Bozec A, Bakiri L, Jimenez M, Schinke T, Amling M, Wagner EF. Fra-2/AP-1 controls bone formation by regulating osteoblast differentiation and collagen production. J Cell Biol. 2010;190(6):1093-106.
20. Wagner EF, Eferl R. Fos/AP-1 proteins in bone and the immune system. Immunol Rev. 2005;208:126-40.
21. Li L, Yang H, He Y, Li T, Feng J, Chen W, et al. Ubiquitin-specific protease USP6 regulates the stability of the c-Jun protein. Mol Cell Biol. 2017;38(2):e00320-17.
22. Huang Z, Fang T, Si Z, Li Y, Zhang L, Zheng C, et al. Imaging algorithm and multimodality evaluation of spinal osteoblastoma. BMC Musculoskelet Disord. 2020;21(1):240.
23. Atkins GJ, Kostakis P, Pan B, Farrugia A, Gronthos S, Evdokiou A, et al. RANKL expression is related to the differentiation state of human osteoblasts. J Bone Miner Res. 2003;18(6):1088-98.
24. Gori F, Hofbauer LC, Dunstan CR, Spelsberg TC, Khosla S, Riggs BL. The expression of osteoprotegerin and RANK ligand and the support of osteoclast formation by stromal-osteoblast lineage cells is developmentally regulated. Endocrinology. 2000;141(12):4768-76.

25. Takami M, Woo JT, Nagai K. Osteoblastic cells induce fusion and activation of osteoclasts through a mechanism independent of macrophage-colony-stimulating factor production. Cell Tissue Res. 1999;298(2):327-34.

26. Cottone L, Ligammari L, Lee HM, Knowles HJ, Henderson S, Bianco S, et al. Aberrant paracrine signaling for bone remodeling underlies the mutant histone-driven giant cell tumor of bone. Cell Death Differ. 2022;29(12):2459-71.

27. Cowan RW, Singh G. Giant cell tumor of bone: A basic science perspective. Bone. 2013;52(1):238-46.

28. Avnet S, Lemma S, Errani C, Falzetti L, Panza E, Columbaro M, et al. Benign albeit glycolytic: MCT4 expression and lactate release in giant cell tumour of bone. Bone. 2020;134:115302.