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Role of Denosumab in the Treatment of Osteoblastoma - A Case Report

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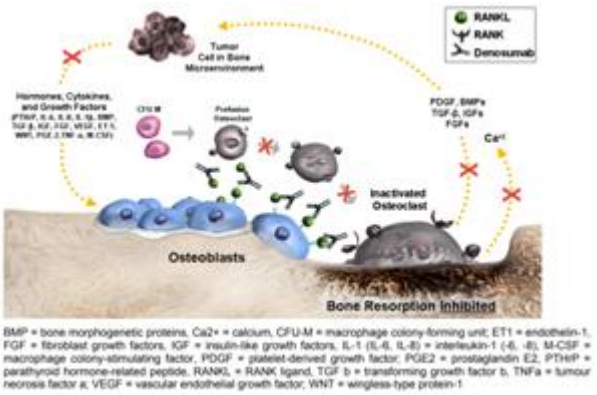
Abstract: ***Introduction: Osteoblastoma is an uncommon osteoid tissue forming the primary neoplasm of the bone. Osteoblastomaarises from osteoblasts. Vertebralcolumn orlongbones are usual sites of presentation, approx. 40% of all osteoblastomaislocated in the spine, and17% of spinal osteoblastomais found in the sacrum. Osteoblastoma of long bones are often diaphyseal; fewer are located in the metaphysis.Denosumabinhibitsthematurationofosteoclastsbybindingtoand inhibiting rank ligand. This protects the bone from degradation and helps to counter the progression of osteoblastoma. Methodology: Two patients with osteoblastoma presented to atertiary Hospitalin the year2018.Both were treated with 120 mg of denosumab subcutaneously on day 0, 8, 15 and 28, after that monthly. Results: Denosumab therapy caused regression of the tumor and converted the diffuse infiltrative mass into a well-defined solid (osteoma like) structure. Conclusion: A short course of denosumab caused tumor regression, ossification, and conversion of an aggressive osteoblastoma into a sclerotic, well-defined lesion and thus aiding surgical resection and preservation of neural structures. Neoadjuvant therapy reduced osteoclast numbers, and this helps to counter the progression of the disease.***

Keywords: Osteoblastoma, Denosumab, RANK-L, Neoadjuvant therapy

1. Introduction

Osteoblastoma is an uncommon osteoid tissue forming the primary neoplasm of the bone. (1)osteoblastoma arises from osteoblasts.(2) they proliferate in an uncontrolled manner and haphazardly produce new bone tissue. It usually presents in the vertebral column or long bones, approx. 40% of all osteoblastoma is located in the spine, and 17% of spinal osteoblastoma is found in the sacrum.(3) osteoblastoma of long bones is often diaphyseal, and fewer are located in the metaphysis. (1)

Pre-osteoclasts, express surface receptors, called RANK (receptor activator of nuclear factor-kappa b), RANK is activated by a RANK Ligand, which exists as cell surface molecules on osteoblasts. activation of RANK by RANK-L promotes maturation of pre-osteoclasts into osteoclasts. (4) denosumab inhibits the maturation of osteoclasts by binding to and inhibiting RANK ligand.(5) this protects the bone from degradation and helps to counter the progression of osteoblastoma.



BMP = bone morphogenetic proteins, Ca2+ = calcium, CFU-M = macrophage colony-forming unit; ET1 = endothelin-1, FGF = fibroblast growth factors, IGF = insulin-like growth factors, IL-1 (IL-6, IL-8) = interleukin-1 (-6, -8), M-CSF = macrophage colony-stimulating factor, PDGF = platelet-derived growth factor; PGE2 = prostaglandin E2, PTHrP = parathyroid hormone-related peptide, RANKL = RANK ligand, TGF b = transforming growth factor b, TNFa = tumour necrosis factor a; VEGF = vascular endothelial growth factor; WNT = wingless-type protein-1

Figure 1: Mechanism of action of denosumab.(5)

2. Literature Survey

In 1932, osteoblastoma (OB) was first described in the English literature by Jaffe and Mayer. Jaffe and Lichtenstein, in 1956, proposed the term "benign osteoblastoma "independently, for identifying an osteoblastic osteoid-forming lesion which is similar to osteoid osteoma (OO) but having greater growth potential. OBs are very rare and constitute about 1% of all primary bony tumors. These tumors tend to involve long bones and vertebral column.(6) The spinal location accounts for 40-50% of all osteoblastoma, from which only 20% located in the cervical spine. The majority of the spinal osteoblastoma arise from the posterior elements: pedicles, laminas, transverse or spinous processes (7).

The time from onset of symptoms to diagnosis is typically several months because it is a rare entity, and radiographic studies are often negative early in the course of the disease. These highly vascular and locally aggressive tumors require complete and precise resection.(8)The cervical spine is a usual localization of osteoblastoma.

The main clinical manifestation in the case of cervical spine location is a progressive and resistant pain, possibly accompanied by stiffness, scoliosis, or other ailments, including severe neurological deficits(9). The sacrum is an uncommon site of involvement(10). Jeremy et al. .reported a Case of 14-year-old male with an aggressive OB affecting the superior articular process of the left first sacral segment, on Denosumab therapy, which caused regression of the tumor and converted the diffuse infiltrative mass into a well-defined solid (osteoma-like) structure, aiding surgical resection and preserving the S1, S4 and S5 nerve roots(3).

3. Aim

To evaluate the role of denosumab when used as

neoadjuvant therapy in the regression of tumor size in osteoblastoma, making it amenable for resection.

4. Materials & Methods

In this prospective study, two patients with osteoblastoma presented to our hospital (KGH, VIZAG) in the year 2018.

a) A 19 yr/m, On CT- aggressive osteoblastoma of S2 vertebra, diagnosis confirmed by HPE of biopsy specimen obtained from S2 vertebral body
b) A 29 yr/f, On CT- medullary expansile lytic lesion of C4 vertebra, diagnosis confirmed by HPE.

Both were treated with 120 mg of denosumab subcutaneously on day 0,8,15 and 28, after that monthly. Informed consent was obtained from both the patients to be as a part of case report.

Radiological images of patient i:

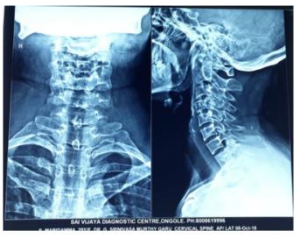


Figure 2 (a): X-RAY –Lytic lesions at C4 vertebra

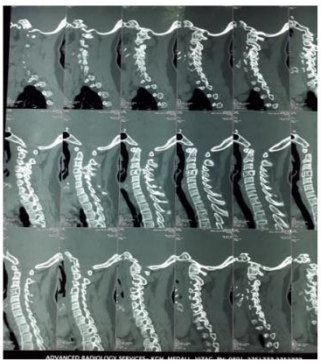


Figure 2(b): CT- Lesion at C4 Level

Radiological images of patient ii:

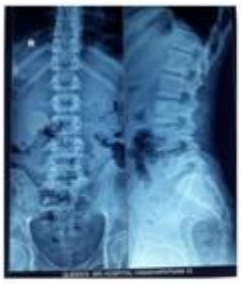


Figure 3 (a): X- RAY LS Spine

Figure 3 (b) : CT –Lesion at S2 Level

5. Observation & Results

Follow up for six months' duration was done for both the patients. The follow-up and monitoring of the patient were done based on radiological findings

Table 1: Radiological findings before and after denosumab therapy

Patient	Radiological findings (Before denosumab therapy)	Radiological Findings (After denosumab therapy)
i. 19 Yr/M	CT: expansile lytic lesion of 25×24 mm(b×l) of s2 vertebral body with extension into neural foramen without obvious softtissue component	sclerotic lesion of 14×23 mm at S2 vertebral body with neural foramen indentation and narrowing
ii. 29 Yr/F	CT: medullary expansile lytic lesion of 41×34 mm with associated cortical thinning of c4 vertebral body with extension into rt vertebral foramen without obvious softtissue component	sclerotic lesion of 29×25 mm at C4 vertebral body with neural foramen extension

6. Discussion

Osteoblastoma is a rare, benign, primary bone-forming neoplasm in which there is an active production of osteoid and primitive woven bone. It was first described as giant osteoid osteoma by Dahlin and Johnson in 1954.(11)Later, Lichtenstein and Jaffe named this tumor in two different articles in 1956.(12)(13)

The peak age of occurrence is between 10 and 20 years, with a range of 6 months to 75 years, and almost 90% occur in the first three decades of life.(14) Osteoblastoma affects males more often than females, with an incidence of 2–3:1. Osteoblastoma has no specific clinic presentation, and the primary complaintis progressive pain, which greatly depends on the location and size.(15)(16)

The involved bone may be expanded and appear as a palpable mass with associated tenderness and swelling. Although osteoblastoma is a slow-growing benign neoplasm, it can also be challenging when it occurs in a difficult location, such as mobile spinal segments or the sacrum as in the spine, it may result in deformities, such as scoliosis and spinal stenosis.

The radiographic presentation of osteoblastoma is also non-specific so that it can be easily misdiagnosed as other benign or malignant bone tumors, but it is necessary to make plain radiographs of the site of pain for the primary diagnosis.

Computed tomography (CT) scanning is often necessary to support the clinical findings because it can identify the lesion, degree of sclerosis, and extent of bony involvement.(17)

The use of MRI can help in defining not only the extent of the osteoblastoma but also the soft tissue involvement, which is superior to CT, but MRI also has a limited role in spinal osteoblastoma because findings can be misleading due to adjacent inflammatory changes.(18)

Some experts believe that both CT scan and MRI should be considered for the preoperative evaluation because although a CT scan is essential to examine the extent of bony involvement correctly, MRI is complementary and should be used when possible to examine the canal, nerve roots, soft tissues, and extraspinal extension.(19) As osteosarcoma could, in some cases, resemble an aggressive osteoblastoma, the exact histopathological differential diagnosismay be difficult, and currently available molecular genetic examinations should be included.

Treatment options include radiation therapy, chemotherapy(20), percutaneous radiofrequency ablation

(RFA),(21) surgery with intralesional margins, surgery with intralesional margins and radiation therapy, surgery with intralesional margins and local adjuvants (phenol or cryosurgical techniques) and resection with wide margins.(22)

The principle of RFA is the utilization of thermal energy to destroy tumor cells and cause coagulation necrosis. When the osteoblastoma is small, lacks aggressive features, and is located in long bones, RFA is preferred, and RFA also should be considered when en-block resection is not feasible, particularly in huge tumors located in difficult surgical areas and recurrent or inappropriately removed tumors(23).

Denosumab is the newest antiresorptive agent with a novel mechanism of action. Denosumab is a fully human monoclonal antibody that inhibits RANKL and helps regulate turnover in healthy bone. Denosumab binds with high specificity and affinity to the cytokine RANKL, inhibiting its action; as a result, osteoclast recruitment, maturation, and action are inhibited, and bone resorption slows.(24)

Denosumab showed positive results in clinical studies of solid tumors with bone metastasis. Denosumab is also useful in other conditions like Giant cell tumor, aneurysmal bone cyst, osteoporosis associated with breast cancer, and prostate cancer. Adjuvant denosumab significantly reduced the risk of clinical fracture risk by 50% in breast cancer patients and by 62% in non-metastatic prostate cancer patients treated with adjuvant aromatase inhibitors or androgen deprivation therapy. Also, biochemical markers of bone turnover and fractures were significantly reduced in patients under denosumab treatment.

7. Conclusion

- A short course of denosumab caused tumor regression, ossification, and conversion of an aggressive osteoblastoma into a sclerotic, well-defined lesion, thus aiding surgical resection.
- Neoadjuvant therapy reduces osteoclast numbers, and this helps to counter the progression of the disease.

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