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Case Report

Severe rebound hypercalcemia following denosumab treatment in a paediatric patient with cervical aneurysmal bone cyst: a case report

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ABSTRACT

Aneurysmal bone cysts (ABCs) are aggressive bone tumours often treated with denosumab, notably when surgical options are minimal. This case report describes an 8-year-old boy who developed severe hypercalcemia following denosumab treatment for a cervical ABC. Initially managed with surgery and chemotherapy, the patient experienced a significant rebound in calcium levels three months after denosumab cessation, leading to symptoms requiring intensive care. Management included intravenous fluids, calcitonin, and zoledronate, resulting in normalization of calcium levels and symptom resolution. This case highlights the need for vigilant monitoring of electrolyte levels and consideration of alternative therapies to prevent rebound hypercalcemia in paediatric patients.

Keywords: Hypercalcemia, Rebound hypercalcemia, Denosumab, Bisphosphonates, Aneurysmal bone cysts

INTRODUCTION

Denosumab is a novel fully humanized monoclonal antibody that binds the nuclear factor receptor kappa ligand (RANK-L) with high specificity and affinity, which further inhibits the interaction between RANK/RANK-L leading to downregulation of osteoclast recruitment, and maturation, as a result attenuating bone resorption. ABCs are benign yet aggressive bone lesions often requiring comprehensive management due to their potential for bone destruction. Dmab has shown promise in the treatment of ABCs particularly in recurrent cases. As the site of action is the extracellular milieu, it has a rapid onset of action, fully reversible and rapid offset of action, cleared by the reticuloendothelial system in approximately twenty-six days. This rapidity causes a sudden surge in osteoclastogenesis responsible for active bone resorption upsetting the equilibrium in the bone multicellular unit.[1] We present a case of an 8-year-old boy who presents with symptoms of hypercalcemia with a history of cervical aneurysmal bone cyst treated with Denosumab in the past, emphasizing the importance of continuous monitoring and strategic therapeutic approaches to mitigate complications and optimize the patient outcomes.

CASE REPORT

An 8-year-old boy with a history of aneurysmal bone cyst (ABC) in the cervical bone s/p excision with residual bone lesions came to tertiary care hospital with chief complaints of history of vomiting, H/o headache, mild and intermittent and history of constipation for a week. Additionally, he had no history of burning on micturition and abdominal pain. No history of fever and loose stools as well. He had a past history of aneurysmal bone cyst

(cervical bone) diagnosed 2 years back, and after excision, he was started on 24 cycles of chemotherapy. Last dose was in August 2023. Residual MRI of the cervical spine was taken, which showed residual lesions and the patient was advised to wait and observe for 6 months. Otherwise, he had a normal developmental history and immunization was up to the age. Examination was unremarkable.

USG abdomen which was done earlier showed colitis; he was managed symptomatically with IV fluids, antiemetics, and IV antibiotics. In account of abdominal pain, a follow up USG abdomen was done which revealed bilateral medical renal disease due to hypercalcemia with normal colon findings. MRI brain showed normal features with no interval changes, whereas bradycardia with ECG changes of metabolic disturbance was noted. 2D echocardiography was done, which was normal. Total body CT scan and X-ray was normal which excluded metastatic disease as a cause of hypercalcemia. Investigations were done which revealed severe hypercalcemia (16.8 mg/dl), elevated uric acid, low potassium, thus the child was shifted to PICU for further management (Table 1). He was treated with two doses of IV calcitonin (80 IU s.c) 24 hours apart. Then he was treated with Zoledronate (0.0225 mg/kg/do). Repeat calcium showed a decreasing trend (12.1 mg/dl). Serial monitoring of Ca level was done and showed decreasing values (8.3 mg/dl). He was additionally given IV and oral KCL and oral magnesium appropriately for correction. On repeat blood work the electrolytes were Calcium 9.3 mg/d, potassium 4.3 mmol/l, magnesium 1.8 mmol/l. ECG changes resolved. The child improved symptomatically, started taking oral feeds. Vomiting and constipation resolved. Thus, was discharged and advised to follow up in two weeks for electrolyte monitoring.

Table 1: Serial investigations of the patient during hospital admission.

Parameters	Reference range	Values					
		December 14, 2023	December 15, 2023	December 16, 2023	December 17, 2023	December 18, 2023	December 19, 2023
Blood urea nitrogen	5–18 mg/dl	53	56	30	-	11	-
Calcium	8.8–10.8 mg/dl	16.8	12.1	10.8	9.2	8.7	8.9
Phosphorus	4.0–5.5 mg/dl	2.4	3.9	4.1	-	-	4.5
Potassium	3.5-5 mEq/l	2.0	2.6	2.5	2.5	3.4	3.6
Magnesium	1.6–2.6 mg/dl	2.0	-	-	1.3	1.2	1.6
Uric acid	2.5–5.5 mg/dl	13.0	10.1	8.0	-	1.4	-

DISCUSSION

RANK-L is a membrane-bound glycoprotein which is a part of tumour necrosis Factor alpha (TNFα) family binds to the RANK receptor and activates diverse mechanisms in the body. This RANK-L is predominantly synthesized by the osteoclasts, osteoblasts and mesenchymal stem cells and T and B lymphocytes, thus marking the key element in bone remodelling. RANK receptor is found in the osteoclast and osteoblast precursor, directing their differentiation. Moreover RANK/RANK-L not only play a part in bone remodelling, it also modulates T cell dendritic interactions, thermoregulation and progesterone derived breast cancer.[2] Normally bone mineral metabolism maintains an equilibrium and adapts to the external factors influencing it via physiological mechanisms in the body. Matrix embedded osteocytes are the major cell type responsible for this well-controlled mechanism within each bone multicellular unit. They control bone formation by expression of Wnt inhibitors sclerostin (SOST) and Dickkopf-1 (DKK-1), and bone resorption via RANK-L and osteoprotegerin as a decoy receptor for RANK ligand.[3,4]

ABC is a benign highly vascular, locally aggressive tumour developed due to impaired hemodynamics which is most common in the first two decades of life. Presence of blood-filled cystic spaces without epithelial or endothelial lining is the hallmark finding of ABC. Traditional treatment options were curettage and bone grafting. Due to the increased incidence of recurrence this is additionally combined with therapies such as selective arterial embolization, radiation and denosumab therapy, these are widely used where the lesions are present in the inaccessible regions like axial skeleton and also in cases with residual lesions.[5]

Denosumab (Dmab) is a human monoclonal antibody that binds to the RANK-L and inhibits the RANK/RANK-L interaction, leading to inhibition of bone resorption. This binds to the RANK-L in the extracellular matrix and washes out from the body within 26 hours, unlike bisphosphonates which binds to the bone osteoclasts network. Dmab technically inhibits the activity of the osteoclasts and thus the turnover of the osteoclasts' precursors slows down but accumulates. Due to the short half-life of the drug, and combined massive indirect

osteoclastogenesis leads to imbalance in the number of osteoblasts and osteoclasts.[6]

This eventually leads to increased bone resorption and derangement in the electrolyte levels in the body, leading to hypercalcemia. This also accompanies other electrolyte derangements such as hypokalemia, hypomagnesemia further inciting injury to the kidney leading to acute kidney injury. There is another hypothesis that intrinsic antibodies develop against Dmab and thus target it, and lead to decrease in serum concentration.[7]

Current literature has a handful of cases and a case series of rebound hypercalcemia as a compilation after cessation of denosumab therapy. Dmab is used for therapeutic management for ABC, central giant cell granuloma, plus other bone osteolysis syndrome which ended up in the successful treatment of the condition but, leading on to the development of rebound hypercalcemia.[8,9] All reported to have developed the condition after four to five months of weaning period, which showed a rapid response with IV bisphosphonates.[10,11] Surprisingly, one case of osteonecrosis of the jaw was found after treatment with Dmab .[12] Not just limited to children, this side effect was also reported in adults who were treated for hyperparathyroidism and metastatic breast cancer.[13]

Primary management of the patient was concentrated on the symptomatic treatment, electrolyte correction, which eventually counteracted the kidney injury. The treatment focused on giving IV fluids, cessation of calcium supplementation, 200 units of calcitonin subcutaneously, followed by IV for rapid decrease in calcium levels and later followed by bisphosphonates due to its late action. The regimen is adjusted according to the current presentation of the patient.[14] In order to alleviate the rebound hypercalcemia a case report highlights that the patient was treated by alternating between Dmab and bisphosphonates every 3 months without any episodes of rebound hypercalcemia. This regimen is still under study as this can be effective in children who may benefit from Dmab.[15] In our case the 8-year-old received the last dose of Dmab in the month of august, and later developed the symptoms of hypercalcemia with acute kidney injury after three months of weaning period. This underscores the importance of taking the electrolyte imbalance into account and adhering to a strict follow up regimen to avoid rigorous complications associated with hypercalcemia.

CONCLUSION

This case report reinforces the value of vigilant monitoring and timely intervention in patients treated receiving Dmab for any condition, especially to rebound hypercalcemia. The severity of the symptoms and inciting injury to the kidney highlights the need for active surveillance of the patient during the weaning period of the treatment. Further studies should focus on strategizing the appropriate treatment protocol to prevent adverse effects and improving the patient outcomes.

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