Turkish Archives of Pediatrics

CASE-BASED REVIEW
DOI: 10.5152/TurkArchPediatr.2025.24189

A Rare Pediatric Giant Cell Tumor of the Clivus Bone, H3.3 p.Gly35Trp-mutated: Case Report and Mini-review of the Literature

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ABSTRACT

Introduction: Giant cell tumor of bone (GCTB) is a rare, typically benign neoplasm that primarily affects long bones in adults, with clival involvement being extremely rare, particularly in pediatric cases: a mini-review shows a total of 28 described cases, of which only 5 were truly pediatric (within 14 years of age). Surgery is the treatment of choice, and Denosumab is reported to be the most effective drug therapy. To date, the GCTB's molecular hallmark is the somatic mutation p.Gly34Trp, at the H3F3A gene (H3.3 p.Gly34Trp mutation), but in this case, the mutation H3.3 p.Gly35Trp was identified.

Case Presentation: A 9-year-old female presented with progressive ocular pain, ptosis, and diplopia. MRI revealed a 42 × 32 × 30 mm mass in the clivus and sphenoid body. The patient underwent partial resection, and histology confirmed GCTB. Molecular testing revealed the presence of the H3.3 p.Gly35Trp mutation, and we demonstrate that this is the true mutation associated with GCTB, not the previously described (H3.3 p.Gly34Trp). Due to residual tumor tissue, the patient was treated with Denosumab, a RANKL inhibitor. During a 2-year follow-up, the tumor size stabilized, and no significant adverse effects were observed.

Conclusion: This case represents the first pediatric clival GCTB harboring the H3.3 p.Gly35Trp mutation. Molecular diagnostics played a crucial role in confirming the diagnosis and demonstrating that the true mutation harbored by GCTB is H3.3 p.Gly35Trp and not the formerly described (H3.3 p.Gly34Trp). Denosumab therapy effectively controlled the tumor without major side effects, although long-term treatment duration and safety require further study.

Keywords: Clivus, bone, giant cell tumor, H3F3A, p.Gly34Trp, p.G35W

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Received: August 19, 2024
Revision Requested: September 17, 2024
Last Revision Received: October 2, 2024
Accepted: October 7, 2024
Publication Date: January 2, 2025

INTRODUCTION

Giant cell tumor of bone (GCTB) is a rare neoplasm that typically occurs in the metaphysis and epiphysis of long bones. The median age of presentation is approximately 35 years. GCTB is extremely rare in pediatric populations, particularly at the base of the skull: only a handful of cases have been reported in pediatric patients, with the majority presenting in adulthood. One of the major diagnostic challenges is the recognition of the molecular characteristics of GCTB: the known mutation associated with GCTB is the H3.3 p.Gly34Trp mutation, which has been reported in approximately 90% of cases.[1,2] However, in this study, we present a pediatric patient with a clival GCTB harboring a distinct but related somatic

Cite this article as: Gaggero G, Battaglia T, Andreotti V, et al. A rare pediatric giant cell tumor of the clivus bone, H3.3 p.Gly35Trp-mutated: case report and mini-review of the literature. *Turk Arch Pediatr.* 2025;60(1):84-91.

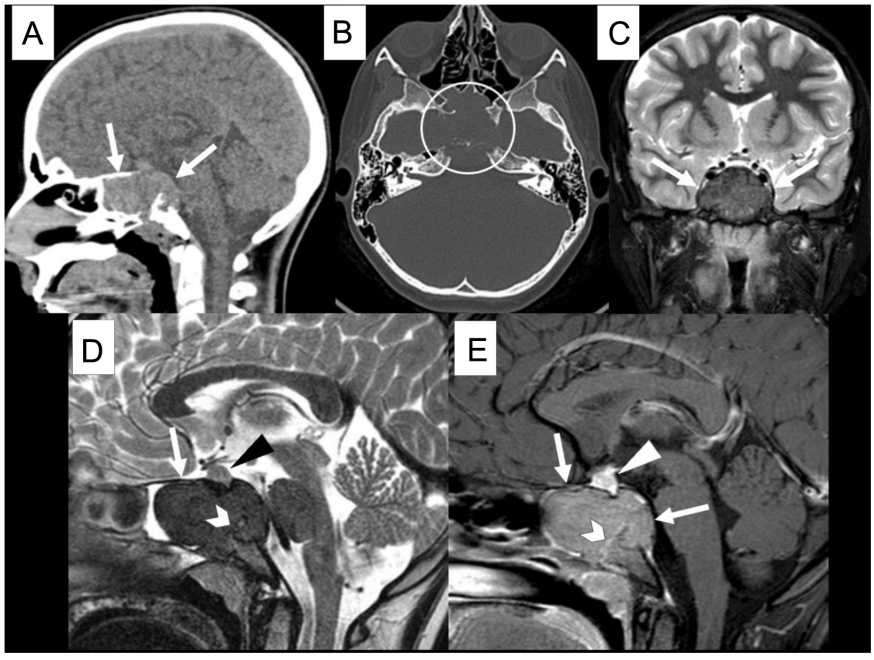

Figure 1. (a) Sagittal soft-tissue window and (b) axial bone window CT scans show a large mass centered in the sphenoid bone, with resorption of the dorsum sellae and posterior sphenoid wall (arrows, a). Notice the extensive bone resorption in the central skull base (circle, b). (c) Coronal T2 short-tau inversion recovery, (d) sagittal T2-weighted image, and (e) contrast-enhanced sagittal T1-weighted images confirm the presence of a large central skull base mass (arrows, d, e), which abuts the posterior fossa posteriorly. Despite its large size, the mass respects the spheno-occipital synchondrosis (arrowheads, d, e) and restricts the pituitary fossa, with elevation of the pituitary gland (triangle, d, e).

mutation, H3.3 p.Gly35Trp. This correction in the mutation nomenclature is significant and further highlights the importance of molecular diagnostics in rare cases.

The aim of this report is to document the first pediatric case of clival GCTB with H3.3 p.Gly35Trp mutation, to demonstrate that the true mutation harbored by GCTB is H3.3 p.Gly35Trp and not the previously described (H3.3 p.Gly34Trp), and to highlight the diagnostic approach, treatment regimen, and clinical outcome after Denosumab therapy.

CASE PRESENTATION

A 9-year-old female presented with progressive bilateral ocular pain, ptosis of the right eye, and intermittent binocular diplopia over several months. Neurological examination revealed no additional deficits, and oculomotor examination, including visual field and evoked potential testing, was normal. Initial magnetic resonance imaging (MRI) revealed a 42 × 32 × 30 mm mass centered on the clivus and extending to the sphenoid body, partially disrupting the spheno-occipital synchondrosis (Figure 1). A full-body computed tomography (CT) scan showed no evidence of distant metastases.

Subtotal resection of the lesion was performed using a transsphenoidal surgical approach. Postoperative neuroimaging revealed residual tumor tissue. Histologic examination revealed a proliferation of mononuclear stromal cells interspersed with scattered multinucleated giant cells consistent with GCTB. Importantly, no necrosis, pleomorphism, or osteoid/chondroid matrix was observed (Figure 2). The differential diagnosis initially considered included non-ossifying fibroma, giant cell

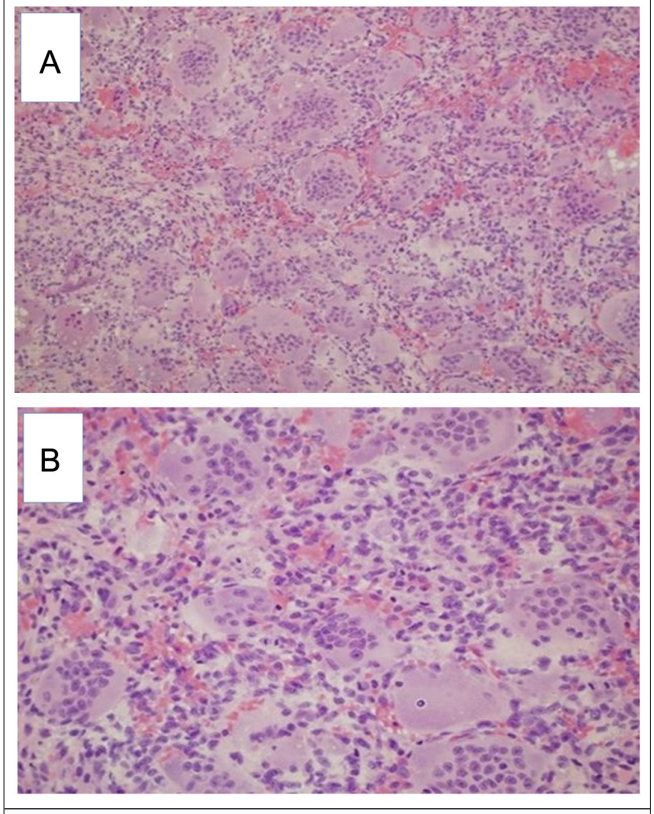

Figure 2. Photomicrograph showing: (a) Several multinucleated giant cells (hematoxylin and eosin staining; magnification 20×). (b) Scattered mitoses in smaller round cells (hematoxylin and eosin staining; magnification 40x).

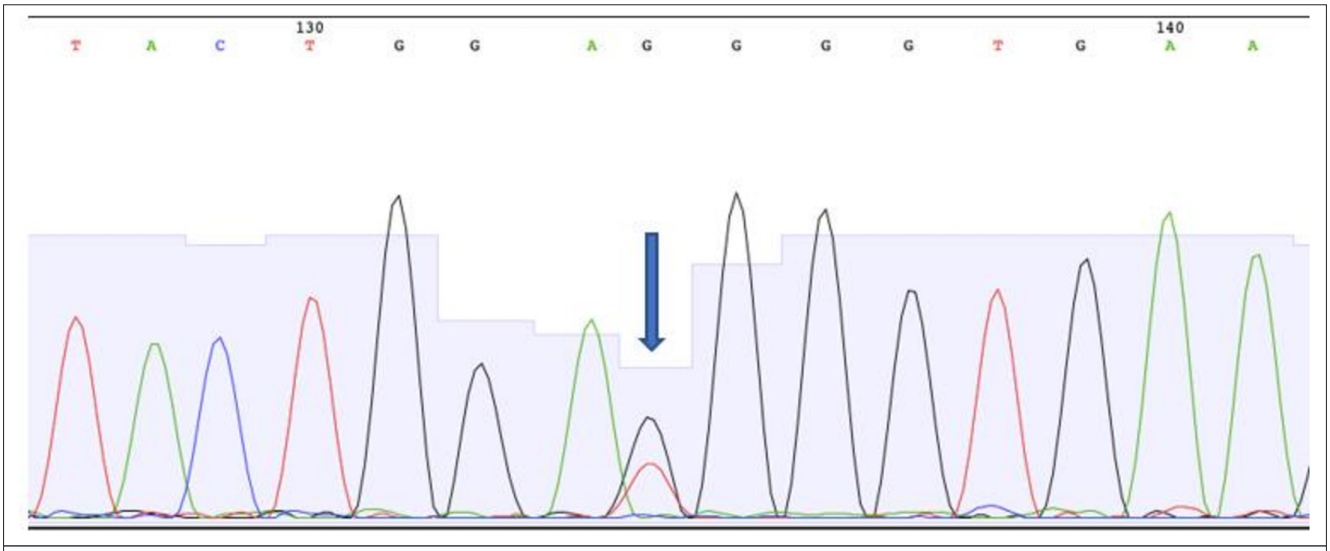

Figure 3. Sequencing electropherogram of a GCTB patient harboring a point mutation, c.103G>T (p.G35W), in the H3-3A gene. DNA was extracted from tumor sections (8 µm) using the Genomic DNA FFPE One-Step Kit for the Diatech MagCore® HF16Plus extractor (RBC Bio-science, Taiwan) according to the manufacturer's instructions. Mutation analysis was performed using PCR amplification of the DNA with a specific intronic primer of exon 2 of H3-3A (LRG_1410, NM_002107.7). Purified PCR products were sequenced using the BigDye Terminator v1.1 cycle sequencing kit (Life Technologies) and a 3130xL Genetic Analyzer (Life Technologies), following the manufacturer's instructions. The electropherogram represents the output from the Sanger sequencing analysis software, identifying a heterozygous missense mutation in the H3-3A gene, c.103G>T (p.G35W). This mutation results from the substitution of G with T, causing a change in amino acid 35 from glycine to tryptophan in the H3-3A protein sequence.

granuloma, brown tumor, and osteosarcoma, but these were excluded based on the histopathologic findings and anatomic location.[1,2]

Molecular analysis of the tumor was performed using PCR and Sanger sequencing. The analysis revealed the presence of a somatic H3.3 p.Gly35Trp mutation (Figure 3): this result raised our curiosity, as the pathogenic molecular variant described in the literature in 90% of GCTBs would be p.G34W (H3.3 p.Gly34Trp mutation).[1] However, we verified that the correct nomenclature of the somatic mutation harbored by GCTBs, referring to the Locus Reference Genomic (LRG_1410; http://www.lrg-sequence.org/) of the H3-3A gene, requires us to describe it as c.103G>T (p.G35W) as also done in a recent case report.[3]

Due to the presence of residual disease and the inoperability of the remaining tumor, treatment with Denosumab was initiated. Denosumab, a monoclonal antibody targeting the receptor activator of nuclear factor kappa-B ligand (RANKL),[4,5] was administered as a subcutaneous injection at a standard dose of 90 mg on days 1, 8, 15, and 28. After three months of therapy, follow-up MRI showed a significant reduction in tumor size, with resolution of brainstem compression. The patient continued Denosumab therapy every 28 days for two months, followed by a reevaluation, which demonstrated stability in the lesion size. Additional cycles of Denosumab were administered every 21 days for four additional administrations, and then every 6 weeks for 1 year.

Review of the Literature

Given the rarity of the diagnosis of GCTB in the clival site and the discrepancy in how this lesion was molecularly recognized in the literature, we proceeded to conduct a literature review on the topic, collecting data to compile a summary table through the articles cited on PubMed (Table 1). The search considered only publications pertaining to primary clivus giant cell tumor (GCT), excluding lesions arising at other sites. Since Wolfe's first description in 1983 (the original publication contains a review of 10 GCTs of the sphenoid bone, including one from clivus),[6] we identified 28 cases of primary GCT of the clivus.[3,6-29] There are four publications in the literature that, in addition to reporting a case report, conduct a review of the previous literature (Zhao, Shibao, Singh, and the last, in 2022, by Pionelli).[3,17,26,29] For the p.Gly34Trp mutation (whose correct nomenclature, as described, is p.Gly35Trp), we included in Table 1 all studies that investigated this mutation by sequencing (thus excluding cases studied only by immunohistochemistry).

DISCUSSION

Giant cell tumor of bone is a rare primary bone tumor that accounts for approximately 5% of primary bone neoplasms.[1] It is typically benign, although a subset of tumors may exhibit aggressive features such as local invasion, recurrence, and, in rare cases, metastasis.[9] The clivus, located at the base of the skull, is an extremely rare site for GCTB, with only 28 cases reported in the literature and only five pediatric cases documented[3,6-29] This case represents the first pediatric case of clival GCTB associated with the H3.3 p.Gly35Trp mutation, highlighting the importance of molecular diagnostics.

Molecular Diagnostics

The H3F3A gene mutation is recognized as a hallmark of GCTB, with most cases harboring the p.Gly34Trp mutation.[1,9] In our case, molecular sequencing revealed a different mutation, p.Gly35Trp, which led to some initial diagnostic confusion due to incorrect nomenclature in earlier reports. The correct nomenclature, based on the Locus Reference Genomic, refers to the mutation as c.103 G>T (p.G35W). This underscores the need for precise molecular analysis in confirming GCTB, particularly in atypical locations such as the clivus, and in younger patients where the diagnosis is especially rare.

Table 1. Literature review on giant cell tumor of bone in the clivus

Patient nr	Reference	Age (years)	Sex	Clinical features	Symptoms (weeks)	MRI imaging	Maximum lesion diameter (cm)	Vascularity	Surgery	RT	Out-come	Follow-up (months)	p.Gly34Trp mutation *(p.Gly35Trp)
1	Wolfe (1983)[6]	16	F	HA, DP, BV	4-7	-	-	-	SR	Yes	Alive, RT	96	Not performed
2	Kattner (1998)[7]	9	F	HA, DP	4	Space-enhancing lesion, T2 hypo- and isointense mass	-	-	Biopsy (TSS)	Yes	Alive, RT	12	Not performed
3	Sharma (2002)[8]	18	F	HA, HL, FP	24	Space-enhancing lesion, T1-isointense, T2-hyperintense	-	Moderate	Near TR	Yes	Alive	12	Not performed
4	Sharma (2002)[8]	12	F	HA, HL right, FP, NR; NT	12	Space-enhancing lesion, T1-isointense, T2-hyperintense	3	Moderate	TR	Yes	Alive	12	Not performed
5	Zorlu (2006)[9]	14	F	HA, DP	10	Space-enhancing lytic expansive mass lesion	6	-	SR	Yes	Alive, RT	24	Not performed
6	Gupta (2008)[10]	17	F	HA, DP, A, VD	24	Space-enhancing lesion	7.6	Moderate	SR	Yes	Alive, RT	24	Not performed
7	Sasagawa (2012)[11]	26	M	HA, DP	-	Space-enhancing lesion, T1-isointense, T2-hypointense	3	High	SR	Yes	Death	9	Not performed
8	Iacoangeli (2013)[12]	31	M	HA, DP	-	Space-enhancing lesion	-	High	Near TR	No	Alive, RT	72	Yes
9	Roy (2013)[13]	19	M	HA, FH	24	T1 large expansile mass, T2-hyperintense	5.6	High	TR	Yes	Alive, RT	18	Not performed
10	Mahale (2013)[14]	20	M	HA, ROP, recurrent transient BN	10	Iso- to hypointense on the T1, T2 and the FLAIR images	6.6	High	Trans-nasal Endoscopy	Yes	Alive	-	Not performed
11	Agrawal (2014)[15]	62	M	HA, DP	12	Space-enhancing lesion	-	-	SR	-	Death	-	Not performed
12	Zhao (2014)[3]	22	M	HA	24	Isointense on T1, T2WI, and fluid-attenuated inversion recovery	4.68	High	Trans-nasal TransSphenoidal Surgery	Yes	Alive	24	Not performed
13	Yildirim (2014)[16]	27	F	HA, DP	48	Enhancing heterogeneously with contrast	5.1	Moderate	Extended Endoscopic Endonasal Approach	Yes	Alive	6	Not performed
14	Shiba (2015)[17]	25	M	DP	4	Space-enhancing lesion, T1-isointense, T2-hypointense	5.1	High	SR	Yes	Death	31	Not performed

Patient nr	Reference	Age (years)	Sex	Clinical features	Symptoms (weeks)	MRI imaging	Maximum lesion diameter (cm)	Vascularity	Surgery	RT	Out-come	Follow-up (months)	p.Gly34Trp mutation *(p.Gly35Trp)
15	Le (2015)[18]	49	M	HA, BV	2	(only computed tomography)	4.9	-	Le Fort I osteotomy and Median Maxillotomy Approach	Yes	Alive	12	Not performed
16	Inoue (2016)[19]	16	M	HA, tight oculomotor NP	12	Isointense on T1, slightly hypointense on T2	-	-	SR	No	Alive, RT	17	Not performed
17	Goto (2017)[20]	34	M	DP	1	Heterogeneous space enhancing lesion, T1 isointense, T2 slightly hyperintense	-	-	Near TR – Endoscopic Endonasal approach	No	Alive, RT	7	Not performed
18	De la Peña (2017)[21]	34	M	HL right, DZ, T, right facial NP	12	Hyper-intense lesion	-	-	Temporal Craniotomy and TransNasal TransSphenoidal Surgery	Yes	Alive, RT	48	Not performed
19	Patibandla (2017)[22]	20	M	Left HC, HA, V, drooping of left eyelid	6	T1/T2 isointense	-	-	SR	Yes	Alive, RT	3	Not performed
20	Satapathy (2018)[23]	24	M	HA, DP, VD	16	Space-enhancing large mass centered on clivus	5.7	Moderate	TR	Yes	Alive	8	Not performed
21	Scotto di Carlo (2018)[24]	55	F	HA, V	-	Space-enhancing lobulated mass originating from the clivus	5	-	Suboccipital approach and redo surgery	Yes	Alive	36	Yes
22	Huh (2018)[25]	18	F	HA, DP	4	Heterogeneously enhancing, hyperintense lesion in the upper clivus	-	-	Endoscopic Endonasal Aprroach	No	Alive, RT	12	Not performed
23	Singh (2020)[26]	35	F	HA, DP, BV	24	Space-enhancing lesion, homogenously enhancing space-accupying lesion	4	High	SR Endonasal Endoscpic TransSphenoidal	Yes	Alive, RT	6	Not performed
24	Tanikawa (2020)[27]	15	M	DP	8	Space-enhancing lesion in the sphenoid sinus with bone erosion	-	-	SR	No	Heterogeneous	60	Not performed
25	Yprak Bayrak (2021)[28]	23	M	HA, VL	-	Necrotic sella mass on T1	4.0	-	Endoscopic TransSphenoidal surgery	Yes	Alive	14	Not performed
26	Yprak Bayrak (2021)[28]	11	F	VL	-	Heterogeneous contrasting mass lesion	-	High	Endoscopic TransSphenoidal surgery	Yes	Alive	5	Not performed

(*Continued*)

Table 1. Literature review on giant cell tumor of bone in the clivus (*Continued*)

Patient nr	Reference	Age (years)	Sex	Clinical features	Symptoms (weeks)	MRI imaging	Maximum lesion diameter (cm)	Vascularity	Surgery	RT	Out-come	Follow-up (months)	p.Gly34Trp mutation *(p.Gly35Trp)
27	Pionelli (2022)[29]	14	F	HA, VD, DP, LP	2	Heterogeneous space-enhancing lesion, T1 isohypointense	5.5	-	SR	No	Alive, RT	30	Not performed
28	Hu (2022)[30]	20	M	Right eye LA only	2	Isointensity on the T1 and T2	2.4	High	Endoscopic Endonasal Approach	Yes	Death	28	Not performed

A, amenorrhea; B, biopsy; BN, bleeding nose; BV, blurred vision; DP, diplopia; DZ, dizziness; F, female; FH, facial hyperesthesia; FP, facial paresis; HA, headache; HC, hemicrania; HL, hearing loss; LA, limited abduction; LP, left ptosis; M, male; NP, nerve palsy; NR, nasal regurgitation; NT, nasal twang; ROP, retro-orbital pain; SR, subtotal resection; T, tinnitus; TR, total resection; V, vomiting; VD, visual disturbance; VL, vision loss.

Molecular diagnostics in GCTBs are crucial for distinguishing between different tumor subtypes, guiding treatment decisions, and improving prognostic accuracy. The discovery of this specific mutation further adds to the body of evidence supporting the use of targeted molecular analysis as part of the standard diagnostic approach for GCTBs, particularly in cases where histology alone may not be definitive.

Treatment with Denosumab

Denosumab has emerged as a key therapeutic option in the management of GCTB, especially in cases where surgery is not feasible or where there is residual disease following resection.[4,5,32-35] The mechanism of action of Denosumab involves inhibition of RANKL, thereby preventing the activation and formation of osteoclasts, which are responsible for bone resorption in GCTBs. This case demonstrates the effectiveness of Denosumab as a neoadjuvant therapy, reducing the size of the tumor and stabilizing the residual disease over a two-year follow-up period without significant side effects.

The decision to continue Denosumab therapy was based on the patient's positive response, as evidenced by tumor stability on imaging and the lack of significant adverse events such as osteonecrosis of the jaw or severe hypocalcemia.[29,32-35] However, it is important to note that while Denosumab is effective in controlling tumor growth, it does not address the neoplastic stromal cells that drive GCTB proliferation. This limitation highlights the need for continued monitoring and the potential for future therapeutic interventions, including bisphosphonates or surgical resection, should the tumor become operable.

In pediatric cases, Denosumab has shown promise, but long-term data on its safety and efficacy are still limited. Side effects such as arthralgia, fatigue, and hypercalcemia have been reported in adult patients undergoing prolonged therapy, and careful consideration must be given to the potential for cumulative toxicity in younger patients. The optimal duration of Denosumab treatment remains unclear, and further research is needed to establish guidelines for long-term use, particularly in pediatric populations.[34]

CONCLUSION

This case report represents the first-documented instance of a pediatric clival GCTB with the H3.3 p.Gly35Trp mutation. Molecular diagnostics played a crucial role in confirming the diagnosis and demonstrating that the true mutation harbored by GCTB is H3.3 p.Gly35Trp and not the formerly described (H3.3 p.Gly34Trp), while Denosumab therapy proved effective in controlling the residual tumor over a two-year period. Although the optimal duration and long-term safety of Denosumab therapy are still uncertain, this case provides valuable insights into the management of GCTB in pediatric patients and highlights the need for ongoing research into both the molecular characteristics of GCTB and the development of novel therapeutic strategies.

Availability of Data and Materials: The data supporting the findings of this study are available within the article and/or its supplementary materials.

Informed Consent: This study is entirely retrospective and observational, based on existing literature. Informed consent is not required, as patients at IRCCS Istituto Giannina Gaslini provide a consent upon admission.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – G.G., T.B.; Design – G.G.; Supervision – V.G.V.; Resources – C.M.; Materials – G.G., V.A., A.R., C.M.; Data Collection and/or Processing – M.I., D.T.; Analysis and/or Interpretation – G.G.A.R.; Literature Search – M.I., D.T., T.B.; Writing – G.G., T.B., V.A., A.R., G.P.; Critical Review – V.G.V.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study received no funding.

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