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Case Report

Successful treatment of adult cherubism with a 60 mg denosumab 6-monthly regimen

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Abstract

Cherubism is a rare autosomal dominant skeletal dysplasia, affecting the maxilla and/or mandible. The condition typically has childhood onset, followed by progression until puberty, with subsequent regression. Cherubism lesions share histological features with giant cell tumor of bone, where high-dose monthly denosumab is an effective medical treatment. Therefore, high-dose denosumab has also been trialed in children with cherubism with positive outcomes. However, the role of denosumab in adult cherubism, particularly a lower dose and frequency, has not been established. We present the case of a 60-year-old man with cherubism, reviewed for a new 39 × 21 mm left mandibular lesion. The patient had multiple surgeries up to the age of 30 for tumors in the right maxilla and mandible. Given the impact of further surgery on his appearance and quality of life, the patient was referred to Endocrinology for consideration of medical therapy. His bone turnover markers were slightly elevated with normal calcium, phosphate, 25-OH vitamin D, and parathyroid hormone levels. A bone density scan showed lumbar spine osteopenia. He was commenced on 60 mg denosumab 6-monthly with excellent clinical and radiological responses over the next 30 months. The most recent CT mandible showed a sustained reduction in the lesion size, measuring 36 × 18 mm, with osteoid formation and improvement in cortical thinning. Surgery is no longer indicated. No adverse effects from denosumab were reported in the patient. This is the first study to report the efficacy and safety of a low-dose denosumab regimen in the management of cherubism. This treatment approach was able to prevent major surgery and minimize denosumab-related adverse effects. While the optimal treatment duration remains unclear, the patient will continue with 60 mg denosumab 6-monthly in the short-term given the favorable response. In summary, a low-dose denosumab regimen should be considered for patients with cherubism, particularly those with contraindications or preferences to avoid surgery.

Keywords: cherubism, giant cell tumor, osteoclast, denosumab, antiresorptive therapy, *SH3BP2*, adult

Lay Summary

Cherubism is a rare genetic condition with jawbone tumors. The condition typically starts in childhood and improves after puberty. Cherubism shares features with a condition named giant cell tumor of bone, where high-dose monthly denosumab is an effective treatment. Therefore, high-dose denosumab has also been trialed in cherubism with positive outcomes in children. However, the role of denosumab in adults with cherubism has not been established. Additionally, it is unclear if cherubism requires high-dose denosumab, as giant cell tumor of bone is more aggressive. We present the case of a 60-year-old man with cherubism who was reviewed for a new left jaw tumor. He had multiple surgeries prior to the age of 30 years for a right jaw tumor. Given the impact of further surgery on his appearance and function, the patient was trialed on low-dose 60 mg denosumab 6-monthly instead. Over the next 30 months, he has demonstrated good response with shrinkage of the tumor and new bone formation. No side effects occurred. Given these findings, we recommend that 60 mg denosumab 6 monthly should be considered for other patients with cherubism for tumor control while minimizing medication side effects.

Introduction

Cherubism is a rare skeletal dysplastic condition, characterized by the presence of fibro-osseous lesions in the mandible and/or maxilla.[1,2] Clinical signs, including facial swelling and deformities, are detected at the age of 2-7 years. Typically, the condition progresses until puberty, followed by regression thereafter.[3] Rarely, extracranial manifestations have been reported.[2] In most patients, cherubism is due to gain-of-function mutations in the *SH3BP2* gene, and thus genetic testing is recommended in all suspected cases.[4] Inheritance follows an autosomal dominant pattern, and family history is evident in the majority of cases.[1]

Histologically, cherubism lesions contain numerous osteoclast-like multinucleated giant cells in fibrous stroma, likely from excess osteoclastogenesis in response to receptor activator of nuclear factor kB-ligand (RANKL) stimulation.[5] These features are not specific to cherubism and may also be observed in other giant cell tumors, such as central giant cell granuloma (CGCG) of the jaw and giant cell tumor of bone (GCTB).[6]

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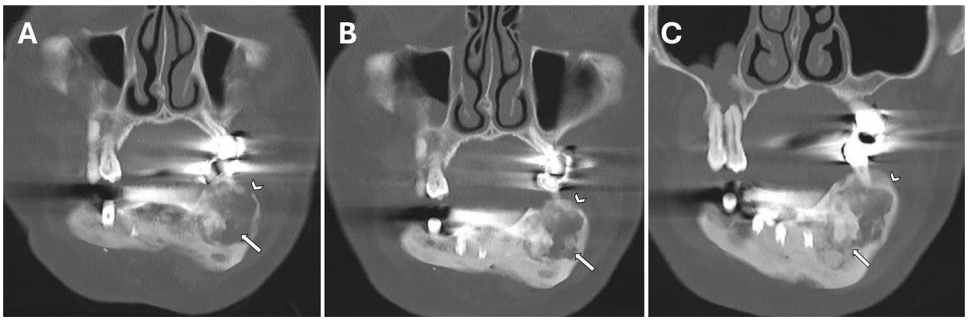

Figure 1. Coronal CT in bone windows through the mandible at the level of the giant cell tumor. (A) Prior to denosumab commencement: A large lytic lesion with endosteal scalloping (arrow) involving the mandibular dental roots and a focal region of cortical demineralization (arrowhead). (B) Six months after denosumab commencement: Progressive infilling of the tumor with osteoid post treatment (arrow) and cortical new bone formation and thickening (arrowhead). (C) Thirty months after denosumab commencement: Further progressive tumor osteoid formation (arrow) and healed buccal surface cortical defect (arrowhead).

Denosumab, an anti-RANKL monoclonal antibody, is effective in the management of GCTB and CGCG.[7–11] Given similar histological features, a high-dose denosumab regimen (up to 120 mg monthly) has also been trialed in pediatric patients with cherubism with some success. However, it remains unknown if such a high-dose regimen is necessary, particularly with the potential risks of osteonecrosis of the jaw (ONJ), atypical femoral fracture (AFF), and increased osteoclast activation with treatment interruption. In addition, the role of denosumab in adults with cherubism has not been established. Here, we present the first successful report of 60 mg denosumab 6-monthly in the management of recurrent adult cherubism.

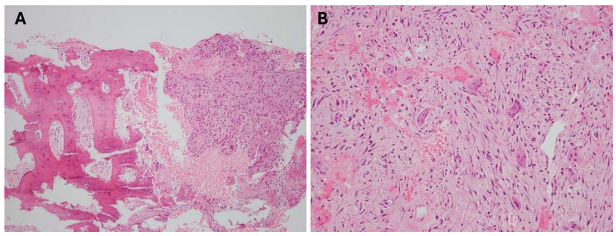

Figure 2. Histopathology of the mandibular giant-cell lesion. (A) Giant-cell lesion on the right within reactive woven trabecular bone (H&E, 10×). (B) Numerous multinucleated giant cells in hemorrhagic cellular stroma (H&E, 20×).

Case description

A 60-year-old man was referred for surgical management of a left expansile mandibular lesion, first noted 15 months prior. He had a supposed history of fibrous dysplasia, diagnosed at the age of 4 years. Multiple maxillofacial surgeries took place in his childhood; however, the exact details were unavailable. Due to tumor recurrence in his twenties, the patient underwent debulking and enucleation of a right maxillary lesion. Subsequently, he required a right hemi-mandible resection and deep circumflex iliac artery (DCIA) bone flap in his late thirties for a further recurrence. The patient's condition remained stable, and no further surgery was required subsequently.

On examination, there was marked swelling of the patient's left mandible, complicated with pain and paresthesia over the mandibular distribution of the left trigeminal nerve. There was no functional limitation from the lesion nor extra-cranial manifestation. Imaging, including orthopantomography (OPG) and cone beam CT, confirmed the presence of a 39 × 21 mm lytic lesion in the left mandible, with endosteal scalloping and cortical thinning. The lesion involved the roots of the left mandibular pre-molars and molars without root resorption (Figure 1A). A biopsy of the lesion demonstrated numerous osteoclast-like giant cells in cellular stroma, consistent with central giant cell granuloma (Figure 2). He was waitlisted for a fourth quadrant soft tissue vestibuloplasty and sulcoplasty. Left mandible resection and reconstruction were reserved as salvage therapies.

Given the impact of surgery on the patient's appearance, daily function, and quality of life, he was referred to the Endocrinology Department for consideration of medical therapies. Further assessment revealed a significant family history of similar jaw lesions, affecting the patient's father, sister, paternal cousins, nephew, and grandnephew. In this context, the patient was referred to Clinical Genetics given suspicion of autosomal dominant cherubism. Genetic investigations confirmed a pathogenic missense mutation of exon 9 in the *SH3BP2* gene (*SH3BP2* NM_001122681.2: c.1253C>G; p.(Pro418Arg)). This result and the bilateral distribution of the lesions support a diagnosis of cherubism, rather than craniofacial fibrous dysplasia. Further investigations showed elevated bone turnover markers: C-terminal telopeptide of type 1 collagen (CTX) was 656 μg/L (reference range 100-600), procollagen type 1 N propeptide (P1NP) was 84 μg/L (reference range 15-84). Calcium (2.43 mmol/L), phosphate (1.12 mmol/L), 25-OH vitamin D (97 nmol/L), and parathyroid hormone levels (6.0 pmol/L) were all within normal ranges. Myeloma screen was negative. DEXA demonstrated osteopenia at the lumbar spine (Table 1) with no previous fractures.

The patient was discussed at a joint Endocrinology and Maxillofacial Surgery multi-disciplinary team meeting. The consensus was for a trial of antiresorptive therapy given the risk of post-operative tumor recurrence. Denosumab was chosen due to favorable results in case reports of pediatric cherubism and its role in the local treatment protocol for GCTB.[12] The patient was commenced on 60 mg denosumab subcutaneously every 6-monthly, with possible dose escalation if required. Within a month of the first dose, there was improvement in his mandibular swelling, pain, and paresthesia. Repeat CT mandible 6 months later showed slight reduction in the lesion size, measuring 36 x 18 mm (Figure 1B).

Table 1. DEXA scan results.

	Prior to denosumab			2 yr after denosumab commencement			% change in BMD
	BMD (g/cm^2)	*T*-score	*Z*-score	BMD (g/cm^2)	*T*-score	*Z*-score	
Lumbar spine (L1-L4)	0.974	−1.1	−0.4	1.050	−0.4	0.3	+7.8%
Femoral neck	0.866	−0.5	0.5	0.923	−0.1	0.9	+6.6%
Total hip	1.007	−0.2	0.3	1.028	0.0	0.4	+2.1%

There was evidence of osteoid formation, improvement in cortical thinning, and interval extraction of a premolar.

At present, the patient has had five 6-monthly doses of 60 mg denosumab. He has tolerated denosumab well without complications, including hypocalcemia, hypophosphatemia, ONJ, or fractures. His jaw swelling and pain remain well-controlled. Recent CT of the mandible showed a stable 36 x 18 mm left mandibular lesion, with marginal increase in osteoid formation (Figure 1C). The extraction defect has healed well with new bone formation. Biochemically, bone turnover markers remained suppressed (CTX < 70 ng/L and P1NP 10 μg/L) with normal 25-OH vitamin D (106 nmol/L) and calcium (2.29 mmol/L) levels. A recent DEXA scan showed significant increases in the lumbar spine and femoral neck density (Table 1). Given good clinical and radiological progress, surgery is no longer indicated. At this stage, the patient will continue 60 mg denosumab 6-monthly with regular endocrinology and maxillofacial surgery reviews. At the time of future denosumab cessation, the risks of tumor growth and rebound loss of bone mass will need to be addressed appropriately.

Discussion

To our knowledge, this is the first case report to demonstrate the efficacy of denosumab as a standalone therapy in an adult with recurrent cherubism, over 30 months of follow-up. Another novel finding was that a low-dose 60 mg denosumab 6-monthly regimen is effective in the management of cherubism.

While there is no consensus guideline on cherubism management, treatment options include longitudinal observation and surgical and medical therapies. The choice of therapy generally depends on the severity of cherubism and patient factors. Milder forms without facial dysmorphology, dental, and ocular involvement may not require treatment, as cherubism is expected to regress spontaneously after puberty in most cases.[13] Surgical interventions, including partial resection, contour resection, and curettage, may be indicated in aggressive cases.[14] Medical therapies, either as adjuvant or standalone therapies, have been trialed in several case reports.[15] Immunomodulatory agents, such as imatinib (a tyrosine kinase inhibitor) and tacrolimus (a calcineurin inhibitor), have demonstrated promising results in cherubism. On the other hand, adalimumab, a monoclonal antibody against tumor necrosis factor-α (TNF-α), was ineffective in preventing tumor progression. Calcitonin had various effects on cherubism; however, its use might be limited by tachyphylaxis, adverse effects, and the availability of other therapies. While bisphosphonates have been trialed successfully in craniofacial fibrous dysplasia, its use in cherubism is limited to only three case reports with unfavorable outcomes. One of the three patients required subsequent treatment with denosumab to achieve adequate tumor control.

The success of denosumab in the management of cherubism can be explained by the underlying pathogenesis of the condition. In an in vitro study, bone marrow cells from *SH3BP2*-mutant mice differentiated into exceptionally large and multinucleated osteoclasts when incubated with RANKL. This occurred even at a RANKL concentration insufficient to induce osteoclast differentiation in wild-type cultures.[5] Denosumab, an anti-RANKL monoclonal antibody, targets the exaggerated RANKL-dependent osteoclastogenesis response in cherubism. This results in inhibition of bone resorption by osteoclastic giant cells, leading to osteolytic lesion suppression and subsequent osteogenic response from local osteoblasts. Therefore, denosumab can be considered a targeted therapy for cherubism.

To our knowledge, denosumab therapy has been used in 5 reported cases of cherubism.[16–19] All patients were either children or adolescents (age ranged 9-19 yr at time of treatment). Two cases were managed surgically prior to medical therapy. Positive clinical outcomes were observed in all cases, including suppression of lesion expansion and/or increased ossification. Denosumab was generally well-tolerated with 2 cases of hypocalcemia and 1 case of hypophosphatemia. There was no report of ONJ, AFF, or fracture after denosumab cessation. Our patient's cherubism was atypical with recurrence in adulthood. While it may be argued that longitudinal observation is an option, given multiple recurrences and the risk of dental fractures, active treatment was more appropriate for the patient. Our study confirmed that denosumab is an effective therapy, clinically and radiologically, for older adults with cherubism.

In all 5 case reports, high-dose denosumab regimens with some variations were used. These patients received 120 mg denosumab subcutaneous monthly, with loading doses on day 8 and 15. This was derived from the treatment protocol for GCTB.[10,11] While GCTB is locally aggressive with the potential to metastasize, cherubism is relatively benign.[20] Therefore, it was unclear if such intensive treatment is required. Indeed, this question was addressed in a study on CGCG, a related benign giant cell tumor.[7] The authors found that a conservative approach with lower-frequency 120 mg denosumab dosing (following a stepwise increase in dosing interval from monthly, to 2-monthly, 3-monthly, and 6-monthly) was effective in all patients, while minimizing potential adverse effects. Our report adds to this study that an even lower-dose regimen with 60 mg denosumab 6-monthly was able to achieve a sustained clinical and radiological response, over 30 months of follow-up. The treatment effect was adequate to prevent major surgery in our patient, and there has been no evidence of denosumab-related adverse effects. Therefore, medical therapy should be considered for patients with

cherubism, particularly those with contraindications or preferences to avoid surgery.

The optimal duration of denosumab therapy in cherubism remains unclear. In the aforementioned 5 case reports, patients received a total of 7-14 doses of denosumab 120 mg (over a total of 6-21 months), without clear rationale for treatment cessation. In CGCG, at least 12 initial doses of denosumab 120 mg should be considered for larger (>30 mm) lesions to minimize the risk of tumor recurrence.[7] For GCTB patients, it was suggested that denosumab should be continued until unacceptable toxicity, disease progression, or patient preference to cease treatment.[12] None of the five patients received bisphosphonates after denosumab cessation, possibly due to their young age and low fracture risks. Currently, our patient planned to continue 60 mg denosumab 6-monthly, acknowledging that there is limited evidence for this approach. Given his age and treatment duration, upon denosumab cessation, the patient will be at risk of rapid bone loss and fracture from rebound osteoclast activation. Therefore, subsequent bisphosphonate treatment and close monitoring of bone turnover markers will be required to mitigate this risk. In addition, longitudinal clinical and radiological assessments for possible tumor growth will be crucial as part of surveillance.

In conclusion, we have presented the first report to demonstrate the efficacy and safety of denosumab in the management of adult cherubism. A low-dose 60 mg denosumab 6-monthly regimen was able to achieve clinical and radiological responses, sustained over 30 mo. Several questions require further investigation, including optimal treatment duration and risk of cherubism recurrence post therapy cessation. Future longitudinal studies are important to further our understanding of this rare condition and its management.

Author contributions

Minh V. Le (Writing—original draft, Writing—review & editing), Felix Sim (Investigation, Writing—review & editing), Kapilan Varatharajah (Writing—review & editing), Asher Goh (Writing—review & editing), and Christopher J. Yates (Investigation, Supervision, Writing—review & editing)

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Conflicts of interest

None declared.

Data availability

Data available on request.

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