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CASE REPORT

Denosumab for craniofacial fibrous dysplasia: duration of efficacy and post-treatment effects

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Abstract

Denosumab has been advocated as a potential treatment for the rare skeletal disorder fibrous dysplasia (FD); however, there is limited data to support safety and efficacy, particularly after drug discontinuation. We report a case of successful treatment of aggressive craniofacial FD with denosumab, highlighting novel insights into the duration of efficacy, surrogate treatment markers, and discontinuation effects. A 13-year-old girl presented with persistent pain and expansion of a maxillary FD lesion, which was not responsive to repeated surgical procedures or bisphosphonates. Pre-treatment biopsy showed high RANKL expression and localization with proliferation markers. Denosumab therapy was associated with improved pain, decreased bone turnover markers, and increased lesion density on computed tomography scan. During 3.5 years of treatment, the patient developed increased non-lesional bone density, and after denosumab discontinuation, she developed hypercalcemia managed with bisphosphonates. Pain relief and lesion stability continued for 2 years following treatment, and symptom recurrence coincided with increased bone turnover markers and decreased lesion density back to pre-treatment levels. This case highlights the importance of considering the duration of efficacy when treating patients with FD and other nonresectable skeletal neoplasms that require long-term management.

Keywords Bisphosphonates · Bone turnover · Hypercalcemia · McCune-Albright syndrome · RANKL

Abbreviations

FD	Fibrous dysplasia
RANKL	Receptor activator of nuclear factor kappa-B ligand
CT	Computed tomography

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Introduction

Fibrous dysplasia (FD) (OMIM #1174800) is a rare, mosaic disorder that results in fractures, pain, and disability. It arises from gain-of-function *GNAS* mutations, encoding the cAMP regulating G-protein $G\alpha_s$ [1]. $G\alpha_s$ activation leads to abnormal differentiation of skeletal progenitor cells and formation of expansile fibro-osseous lesions, which may affect one bone (monostotic FD) or multiple (polyostotic FD). FD may occur in isolation or in conjunction with hyperfunctioning endocrinopathies and hyperpigmented skin macules, termed McCune-Albright syndrome [2]. The craniofacial area is commonly involved, and FD lesion expansion can lead to important clinical sequelae, including optic neuropathy, hearing loss, and facial asymmetry [3, 4].

The mainstay of treatment in FD is surgery to prevent, diminish, and eliminate skeletal deformities [5]. Lesions are typically too widespread for total resection, and standard techniques used in other disorders, such as curettage and grafting, are often ineffective [6]. There is thus a critical need to develop medical treatments capable of reducing FD lesion activity and progression. Bisphosphonates have been advocated due to

high levels of osteoclastogenesis in FD tissue; however, there is no evidence that they have direct lesional effects [7, 8]. Denosumab is a monoclonal antibody to receptor activator of nuclear kappa-B ligand (RANKL), a central regulator of bone resorption, that has shown efficacy for treatment of giant cell tumors, another disorder of skeletal progenitor cells [9]. Emerging evidence suggests that RANKL may play a mechanistic role in FD pathogenesis [10, 11], providing additional support for potential therapeutic use of denosumab. However, denosumab's inhibitory effects on bone turnover are fully reversible after drug discontinuation, representing an important limitation in disorders (like FD) where long-term efficacy is desired. Denosumab discontinuation has also been associated with rebound bone turnover to above pre-treatment levels, leading to rare cases of hypercalcemia [12]. Investigation of denosumab efficacy, duration, and post-treatment effects is therefore critical to determine if and how it can be used safely in FD.

We report a case of successful denosumab treatment for aggressive craniofacial FD with an emphasis on treatment and post-discontinuation effects, including duration of efficacy and bone turnover rebound.

Patient and methods

Denosumab initiation and treatment

A 13-year-old girl presented for consideration of denosumab therapy due to progressive craniofacial FD expansion involving the left palate, nasal bones, maxilla, zygoma, sphenoid, and orbit. She was diagnosed with FD at age 6 years after developing a palatal mass, which was confirmed via biopsy and *GNAS* testing. A bone scan showed no evidence of polyostotic FD, and workup for extraskeletal features showed no endocrinopathies. At age 8 years, she underwent surgical debulking and recontouring due to progressive lesion expansion with pain, facial asymmetry, nasal airway obstruction, sinusitis, rhinorrhea, epiphora, and proptosis. Her symptoms initially improved but returned 1 year later, corresponding with FD regrowth. Over the next several years, she received treatment with pamidronate and zoledronate which improved her pain but did not prevent further aggressive FD expansion. The patient developed severe proptosis resulting in vision changes, in addition to continued facial pain, rhinorrhea, and epiphora. She underwent additional debulking and recontouring procedures at ages 10, 11, and 13 years involving the palatal mass, nose, nasal passages, zygoma, and orbit to restore function and symmetry although aggressive lesion regrowth resulted in symptom recurrence. Following surgery at age 13, the decision was made to initiate a trial of denosumab with the goal of preventing post-surgical regrowth.

FD tissue from a pre-treatment debulking procedure showed typical features of FD, including discontinuous curvilinear trabeculae interspersed with fibrous tissue and numerous osteoclasts (Fig. 1). Fibroblastic cells stained positive for Ki67 and RANKL in association with RANK+ osteoclasts, consistent with highly proliferative FD.

Denosumab was initiated at 53 mg (approximately 1mg/kg) every 4 weeks, with monthly dosing for 18 months, adapted from dosing in giant cell tumors [13]. The dose and interval were gradually increased to 70 mg every 6 weeks, 7 weeks, 8 weeks, and 3 months for a total of 31 doses over a

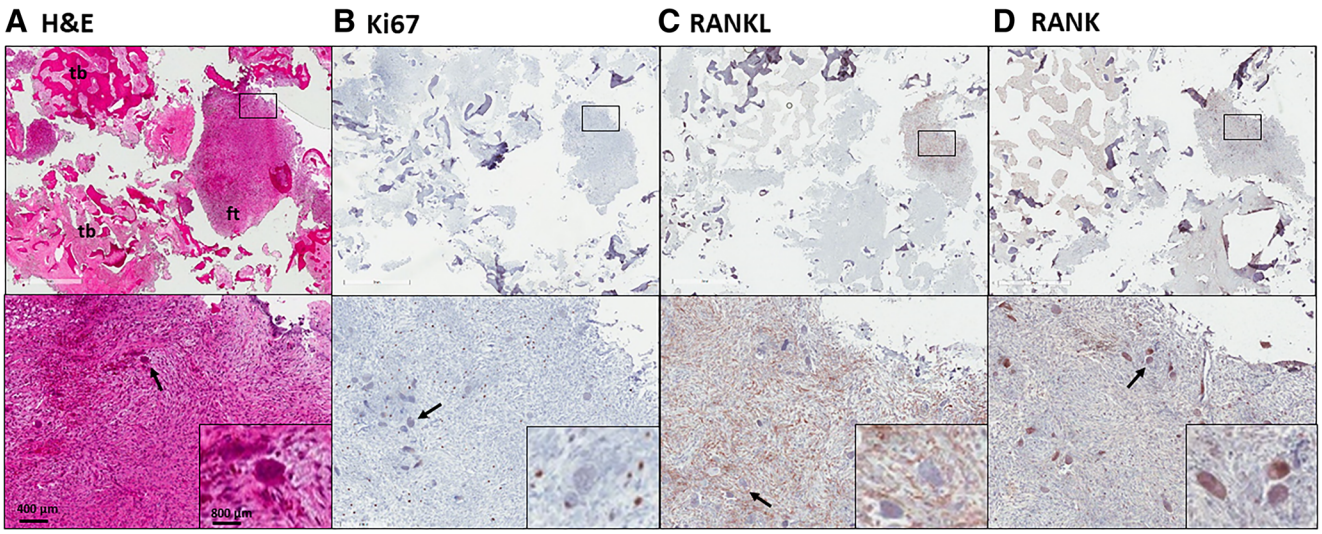

Fig. 1 Fibrous dysplasia serial sections with immunostaining. **a** Hematoxylin and eosin staining shows typical features of fibrous dysplasia, including discontinuous curvilinear trabecular bone (tb) amidst fibrous tissue (ft) comprised of proliferative skeletal progenitor cells. The tissue is highly cellular, consistent with active disease. Note the presence of prominent ectopic osteoclasts residing within fibrous tissue (black arrows and magnified insets). **b** Immunohistochemical staining for cell proliferation marker Ki67 is closely localized with **c** RANKL-overexpressing fibrous cells and **d** RANK-expressing ectopic osteoclasts

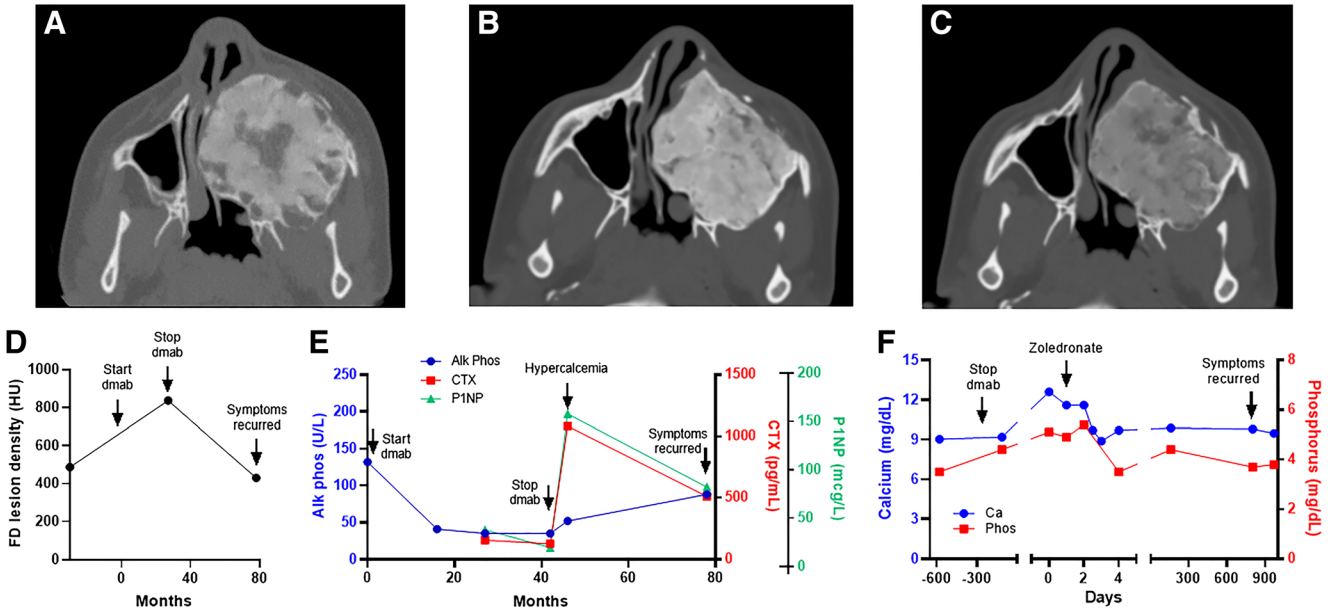

Fig. 2 Radiographic and biochemical response. **a** Axial view from a CT scan obtained 2 years prior to debulking and denosumab initiation shows aggressive expansion into the nasal airway. Note the heterogeneous appearance, with "ground glass" density interspersed with more radiolucent areas. **b** After 2 years of denosumab treatment, the lesion has a more homogeneous, radiodense appearance. **c** At the time of symptom recurrence 2 years after denosumab discontinuation, the lesion has increased slightly in size, with further expansion into the nasal airway. The appearance of the lesion is less radiodense with the formation of additional lucent areas. **d** Graph showing Hounsfield units from the computed tomography scan slices depicted in sections **a**–**c**. **e** Changes in bone turnover markers before, during, and after treatment. **f** Changes in serum calcium and phosphorus during and after treatment

3.5-year period. Shortly after initiation, she reported improvement in pain, and bone turnover markers declined rapidly and remained low for the duration of treatment (Fig. 2e). Calcium levels were collected at the time of each denosumab dose and remained stable within normal limits for the duration of treatment (Fig. 2f). A computed tomography scan after 2 years of treatment showed no further FD expansion and increased lesion density (Fig. 2b, d).

Post-discontinuation effects

Denosumab was continued for a total of 3.5 years. The decision to discontinue therapy was made based on stabilization of her FD lesion, resolution of pain, and progressive increase in extracranial bone density (total body less head Z-score +3.5, AP Spine L1-L4 Z-score +3.0). Labs 1 month following discontinuation showed calcium levels within normal range (9.2 mg/dL) (normal 8.6–10.4 mg/dL). Monthly labs were recommended to monitor bone turnover and serum calcium levels; however, the next time she presented was 5 months after denosumab discontinuation with symptoms of nausea and vomiting. Labs confirmed hypercalcemia (12.6 mg/dL), suppressed PTH (6 pg/mL) (normal 15–65 pg/mL), and increased bone turnover markers C-telopeptides and procollagen 1-propetide (Fig. 2e, f), consistent with severe bone turnover rebound. She was admitted for intravenous hydration and received a 2-mg zoledronate infusion, which resolved her hypercalcemia the following day. After maintaining stable calcium levels within normal ranges for 2 days, she was discharged. Follow-up labs 5 months later showed stable normal levels of calcium, phosphate, and improved PTH (20.4 pg/mL).

The patient remained asymptomatic for 2 additional years, before again noting bone pain and lesion growth in her palatal area. Imaging confirmed a slight interval increase in lesion size, and lesion density decreased to pre-treatment baseline (Fig. 2c, d). Labs showed increased bone turnover markers back to pre-treatment levels (Fig. 2e). DXA scan showed an interval decrease in extracranial bone density (total body less head Z-score +1.8, AP Spine L1-L4 Z-score +1.6). Denosumab was restarted.

Discussion

In this patient with aggressive craniofacial FD, denosumab was effective in managing lesion growth and pain for a total of 5.5 years (3.5 years on- and 2 years post-treatment). Post-treatment bone turnover rebound resulted in hypercalcemia, which was effectively managed with zoledronate. The patient's therapeutic response was accompanied by effects on bone turnover markers and FD lesion density, which paralleled both her improvement in symptoms on-treatment and her return of symptoms post-treatment.

A small but growing body of literature suggests beneficial effects of denosumab in FD, including case studies reporting

potential reductions in lesion expansion [14, 15] and a recent series of 12 adults reporting improved pain and bone turnover markers [16]. However, the lack of available post-discontinuation data represents an important barrier to routine use. This is particularly relevant given that FD and other nonresectable skeletal neoplasms require long-term control, making the reversibility of denosumab's therapeutic effects a central consideration. This case is the first to report the duration of therapeutic effects after denosumab discontinuation in FD. In this patient, denosumab treatment was overall well-tolerated, resulting in a substantial period of symptom relief.

Adverse effects of denosumab in this patient included high extracranial bone density. This is a predictable outcome in skeletal neoplasms, where systemic therapy is necessarily accompanied by reduced turnover in the non-pathologic bone. This patient did not have a pre-denosumab DXA scan for comparison, which would have revealed effects of her prior bisphosphonate treatment. Fortunately, denosumab's effects on non-FD bone were reversible, and the patient's bone density normalized prior to re-initiating treatment, indicating that most of her high bone mass was likely attributable to denosumab. Clinicians should consider obtaining DXA scans prior to initiating denosumab or other anti-resorptive agents and monitor scans periodically during and after treatment.

This is the second report of post-denosumab hypercalcemia in FD patients [14], indicating this population is likely at higher risk due to their high pre-treatment bone turnover. Our patient did not present for standard interval labs; however, regular monitoring of serum and urine calcium levels is important to detect and treat hypercalcemia prior to the development of symptoms. In addition, monitoring bone turnover markers (procollagen-1 propeptide and C-telopeptide) is helpful in determining the presence and timing of post-discontinuation rebound. Bisphosphonates were effective in managing hypercalcemia, suggesting that, like in osteoporosis, patients with FD may benefit from preventative bisphosphonate treatment at the time of denosumab discontinuation [17].

There is a critical need to develop strategies for long-term denosumab treatment in patients with FD and other nonresectable skeletal neoplasms. The high-dose formulation used in this patient may have beneficial effects on FD activity; however, long-term use carries the risk of skeletal toxicity, particularly in the non-pathological bone. This case provides support for an intermittent approach with repeated courses of high-dose denosumab, with monitoring for rebound and increased lesion growth in-between. Another possibility is continuous treatment with lower and/or less frequent "maintenance" doses, although there is little data to support the efficacy of low-dose denosumab in neoplastic disorders like FD. Studies investigating these regimens are needed, including the potential role for adjuvant bisphosphonates.

This is the first case to report increased FD lesion density with denosumab treatment, measured via CT scan using Hounsfield units. A similar increased density is reported in denosumab-treated giant cell tumors [18], which corresponds histologically with ossification of fibrous tissue [19]. In a mouse model of FD, denosumab treatment leads to mineralized lamellar bone formation, suggesting a similar process may occur [11]. This may have particular significance for the management of appendicular FD, where decreased structural integrity under weight-bearing forces leads to bowing deformities and fractures [1]. Additional studies including pre- and post-treatment biopsies are needed to determine tissue effects of denosumab treatment in FD, including effects on mineralization. There is also a critical need to investigate surrogate disease-specific markers capable of assessing treatment response. ^{18}F-NaF-PET/CT imaging has shown promise as a potential tool to quantify FD lesion activity [20, 21]; future studies of denosumab should consider incorporating this modality.

FD is a heterogeneous disease with a broad clinical spectrum, and individual factors likely influence responses to therapies like denosumab. In children and young adults, FD lesions are active and expansile, while in later adulthood, FD lesions become less active and improve histologically [7, 22]. The rate and duration of FD activity also varies considerably between patients, potentially due to unidentified genetic or environmental factors. The patient in this case is young with actively expanding FD, and biopsy confirmed high proliferative activity and vigorous RANKL expression, potentially explaining her severe phenotype and striking therapeutic response. Individual factors are also likely to impact the duration of treatment efficacy and timing of post-treatment rebound.

In conclusion, we report a successful case of denosumab treatment in a patient with craniofacial FD who maintained efficacy for 2 years post-treatment. This case highlights the importance of considering the duration of post-treatment efficacy when treating FD and other nonresectable skeletal neoplasms that require long-term management. In this patient, bone turnover markers and lesion density measured via Hounsfield units paralleled her clinical response, suggesting these may have some utility as surrogate disease markers. The finding of increased FD lesion density provides preliminary support that denosumab may have direct lesional effects on FD tissue, which should be further investigated in clinical trials. The increased bone density and post-discontinuation hypercalcemia observed in this patient highlight the need for additional investigation into safety and efficacy of denosumab in FD, particularly in the post-discontinuation period. Results of an ongoing prospective trial (NCT03571191) will hopefully provide insights into denosumab's therapeutic use in this population. Until that time, denosumab use in FD should be limited to

clinical trials, and as compassionate use for patients with severely morbid disease not responsive to standard management.

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Declarations

Informed consent The patient in this study was seen as part of a natural history study approved by the Investigational Review Board of the NIDCR, NIH (NCT00001727). Informed assent and consent were obtained from the patient and her guardians.

Conflict of interest NIDCR receives support from Amgen, Inc for an investigator-sponsored study of denosumab for fibrous dysplasia (Alison Boyce, Michael Collins). Layne Raborn, Andrea Burke, David Ebb, and Leonard Kaban report no conflicts of interest.

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