Fibrous Dysplasia and Medication-Related Osteonecrosis of the Jaw

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Purpose: Osteonecrosis of the jaw (ONJ) is an established side effect of intravenous bisphosphonates and other antiresorptive medications. Although bisphosphonates are frequently prescribed for patients with the skeletal disorder fibrous dysplasia (FD), there are no reports of ONJ in this population. This has led some to conclude that patients with FD are at low risk for the development of bisphosphonate-related ONJ.

Patients and Methods: Patients were evaluated as part of a longstanding FD natural history study at the National Institutes of Health.

Results: Of 76 patients with FD who were treated with bisphosphonates, 4 developed ONJ (5.4%). Three patients developed ONJ in areas of FD-affected bone and 1 in an area of normal bone. All 4 patients had features known to be associated with ONJ in the general population, including long-term high-dose intravenous bisphosphonate treatment, periodontal and endodontic infections, and dentoalveolar surgical procedures.

Conclusions: These cases establish ONJ as a potential complication of bisphosphonate treatment in patients with FD. The presence of established risk factors for ONJ in this group of patients with FD suggests that high-risk patients could be identified before the development of ONJ. Clinicians should use caution in prescribing bisphosphonates to patients with FD and should do so only for established indications.

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Fibrous dysplasia/McCune-Albright syndrome (FD/MAS; OMIM 174800) is a genetic disorder arising from somatic activating mutations in GNAS, which codes for the signaling protein G\(_\alpha\).1 This mutation leads to constitutive receptor activation, resulting in increased G\(_\alpha\) signaling and dysregulated cyclic adenosine monophosphate production.2 In the skeleton, GNAS mutations lead to increased proliferation and impaired differentiation of skeletal progenitor cells, resulting in the formation of FD lesions that are highly vascular and prone to expansion, deformity, fracture, and pain.3,4 FD can affect 1 bone (monostotic) or multiple bones (polyostotic) and can occur in isolation or in combination with café-au-lait skin macules and hyperfunctioning endocrinopathies, including precocious puberty, hyperthyroidism, growth hormone excess, hypercortisolism, and renal phosphate wasting. The combination of FD and at least 1 extraskeletal feature is considered MAS.2 FD can affect any area of the skeleton and occurs frequently in the craniofacial area.5 Morbidity in the skull relates primarily to FD expansion, resulting in facial asymmetry and, less commonly, functional deficits, including malocclusion, dental anomalies, and vision and hearing impairment.6,7

The mainstay of treatment for FD is surgical, and there are no medical therapies capable of altering the disease course. Antiresorptive therapy with bisphosphonates has been advocated as a potential treatment because of high levels of osteoclastogenesis present in FD tissue and the established role of bisphosphonates in inhibiting osteoclast function.8 Bisphosphonates inhibit bone resorption by incorporating into the hydroxyapatite crystal and inhibiting osteoclast function when they are taken up by active osteoclasts. This group of drugs is used to treat conditions of excessive bone resorption, such as osteoporosis,9 Paget disease,10 malignancies with skeletal metastases,11 and other skeletal disorders such as osteogenesis imperfecta.12 The role of these medications in the management of FD has not been fully elucidated. Early case reports and small series described subjective improvements in pain and variable effects on the radiographic appearance of FD lesions13-15; however, a placebo-controlled trial of the oral bisphosphonate alendronate showed no effects on pain or FD lesion appearance.16 Currently, there is little evidence to support an effect of bisphosphonates on FD quality or lesion expansion; however, intravenous formulations are generally considered beneficial for FD-related bone pain and are frequently prescribed for this indication.2,17,18

The first cases of bisphosphonate-related osteonecrosis of the jaws (ONJ) were reported in 2003 by Marx15 and 2004 by Ruggiero et al.19 Since that time,
other antiresorptive (denosumab) and anticancer (ie, sirolimus, bevacizumab) medications have been implicated in jaw necrosis; as of 2015, the American Association of Oral and Maxillofacial Surgeons’ Special Committee has relabeled this diagnosis as medication-related osteonecrosis of the jaws.\(^{21}\) Despite the frequent use of bisphosphonates in patients with FD, there are no reports in the literature describing ONJ. This has led to postulation that patients with FD might be at lower risk for ONJ compared with the general population of patients treated with bisphosphonates.\(^{18}\) This article describes 4 patients in the National Institutes of Health (NIH) FD/MAS natural history study who developed ONJ subsequent to bisphosphonate treatment.

**Patients and Methods**

The patients in this report were evaluated at the NIH Clinical Center as part of a longstanding FD/MAS natural history study. All patients gave informed consent, and the protocol was approved by the institutional review board of the National Institute of Dental and Craniofacial Research of the NIH. This study followed the Declaration of Helsinki on medical protocol and ethics.
FIGURE 1 (cont’d). C, Three-dimensional computed tomogram displays facial asymmetry with multiple expansile lesions particularly affecting the right side of the skull. D, Axial computed tomogram shows extensive craniofacial fibrous dysplasia exhibiting the characteristic “ground-glass” appearance with multiple areas of radiolucency. Note the left maxilla and alveolar ridge with extensive fibrous dysplasia involvement encasing the left maxillary first and second molars (arrow; American Dental Association teeth 14 and 15).

Results

Of 146 patients with FD seen at the NIH, 76 (46%) had received treatment with bisphosphonates for management of bone pain. Four patients developed ONJ subsequent to bisphosphonate treatment, and these patients are described in detail.

CASE 1

A 47-year-old woman presented with pain and cold sensitivity 3 months after extraction of the left maxillary second molar. The patient had a history of FD/MAS manifested by severe bony involvement in the craniofacial region, thorax, and femur; café-au-lait

FIGURE 2. Case 1. Dental images. A, Preoperative panoramic radiograph taken before extraction of the left maxillary second molar and 3 months before initial presentation of osteonecrosis. The left maxillary first and second molars are located within fibrous dysplasia bone (arrows). B, Periapical radiograph taken before extraction of the left maxillary second molar (American Dental Association tooth 15). Note the periodontal and endodontic lesion associated with the right maxillary second molar (arrowhead). (Fig 2 continued on next page.)

macules; and MAS-associated growth hormone excess (Fig 1). Her history was noteworthy for numerous craniofacial surgeries, including bilateral optic nerve decompressions and multiple maxillary and mandibular recontouring procedures. Her clinical course was complicated by severe FD-related bone pain unresponsive to over-the-counter analgesics and amitriptyline. At 36 years of age, 11 years before her current presentation, the patient was placed on bisphosphonates for pain management, including a 3-year course of pamidronate 180 mg every 3 months from 36 to 39 years of age, followed by a 6-year course of zoledronic acid 4 mg every 3 months from 39 to 45 years of age.

The patient had an extensive dental history with numerous restorative, endodontic, and periodontal procedures. One year before presentation, the patient’s general dentist observed gingival swelling around the left maxillary first and second molars (American Dental Association [ADA] teeth 14 and 15, respectively) and diagnosed a distal endodontic and periodontal lesion with a probing depth of 12 mm;

**FIGURE 2 (cont’d).** C, Panoramic radiograph taken 4 months after extraction of the left maxillary second molar shows bone resorption and osteosclerosis of the lesion (arrow). D, Gutta percha points within the persistent fistula.

she was noted to have generalized mild chronic periodontitis with localized aggressive periodontitis at the left maxillary molars and purulent exudate from the site. Of note, the left maxilla and alveolar ridge had extensive FD involvement. The patient was referred to a periodontist and was treated with scaling and root planing, gingivectomy, and oral antibiotics. One year later, the patient reported lingering pain in the left maxillary second molar; her general dentist observed periapical radiolucency and prescribed a 1-week course of penicillin V. The patient was evaluated by an endodontist who determined that the left maxillary second molar was non-restorable secondary to the persistent endodontic and periodontal lesion (Fig 2B), and extraction was recommended. The patient was referred to an oral and maxillofacial surgeon for extraction of the left maxillary second molar. Three months after extraction, the patient returned to her oral and maxillofacial surgeon with complaints of cold sensitivity, severe pain, and a nonhealing extraction site. Given her history of bisphosphonate treatment in combination with symptomatic, exposed bone that had been present for longer than 8 weeks, she was diagnosed with stage 2 osteonecrosis (ONJ) of the left posterior maxilla. Radiographically, the left maxillary alveolar ridge was noted to have bone resorption and osteosclerotic areas within the FD lesion (Fig 2A). Of note, the patient had discontinued zoledronic acid 2 years before undergoing extraction and received 1 additional dose of zoledronic acid 2 weeks before her ONJ diagnosis. After her ONJ diagnosis, local debridement was performed 3 times during the next year. She was treated with oral cephalexin. Cultures obtained on 2 occasions did not exhibit a predominant species. Ten months after her ONJ diagnosis, the maxillary left first molar (ADA tooth 14) was found to be mobile and showed periodontal compromise (Fig 2C). This tooth was surgically extracted, and the area was debrided. Postoperatively, oral hygiene was stressed, and the patient was prescribed fluoridated toothpaste and triannual dental prophylaxis. Two months after extraction of the left maxillary first molar, the patient reported improved healing and some soft tissue coverage. One year after extraction of the left maxillary first molar, the patient presented with pain and discomfort; a panoramic radiograph showed a persistent fistula (Fig 2D). The patient received cephalexin and reported pain relief. Two years later, the patient again presented with pain and swelling. An intraoral examination disclosed moderate erythema of the mucosa around the lesion with no discharge. Two days later, the patient underwent an incision and drainage. At that time, she was placed on a long-term course of oral antibiotics; however, compliance has been intermittent, and 5 years after her initial diagnosis, she continues to have active ONJ.

FIGURE 3. Case 2, clinical and dental images. A, Technetium-99 bone scan highlighting areas of increased radiotracer uptake in bone (arrowheads) affected by fibrous dysplasia in the skull and bilateral femurs, humeri, and fibulas. (Fig 3 continued on next page.)

FIGURE 3 (cont’d). B, Clinical photograph depicting facial dysmorphism resulting from mild vertical dystopia and diffuse expansion of maxillary and mandibular fibrous dysplasia. C, Three-dimensional computed tomographic reconstruction visualizes diffuse craniofacial involvement with fibrous dysplasia. (Fig 3 continued on next page.)

CASE 2

A 23-year-old man with intellectual disability and FD/MAS presented for routine dental consultation. His disease burden included extensive polyostotic FD involving the skull, proximal humerus, bilateral ribs, and femurs (Fig 3). Additional features of MAS included neonatal hypercortisolism treated with bilateral adrenalectomy, hyperthyroidism treated with total thyroidectomy, and pancreatic intraductal papillary mucinous neoplasms treated with pancreatoduodenectomy. His clinical course was complicated by postoperative right-side vision loss after a prophylactic right optic nerve decompression at 5 years of age. He has a history of severe FD-related bone pain treated with zoledronic acid 4 mg every 3 months from 18 to 23 years of age.

The patient’s complex dental history included orthodontic treatment to correct his malocclusion, starting with a palatal expander 1 year before his current presentation. During orthodontic treatment, the patient sustained a traumatic fracture of the maxillary left lateral incisor. The family requested that the orthodontic appliance be removed owing to difficulty in maintaining oral hygiene. When the appliance was removed, extensive decay was noted on all the maxillary and mandibular anterior teeth (Figs 4A,B). During a routine dental consult at the NIH, a 3- to 4-mm circular area of exposed bone was noted on the left palate adjacent to the left maxillary second and third molars (ADA teeth 15 and 16; Fig 4C). Remarkably, the area of exposed bone was in an area of FD, but did not occur in an area that had been covered by the palatal expander. In addition, the left maxillary third molar was decayed to the gingival margin, and numerous caries were noted throughout the dentition. Neither the patient nor

FIGURE 4. Case 2, intraoral photographs. A, B, Photographs of the anterior maxillary and mandibular teeth, respectively, illustrate rampant dental caries and stagnant plaque after removal of the patient’s braces and the fractured maxillary left lateral incisor. (Fig 4 continued on next page.)

his family was aware of the lesion or the carious tooth, and the patient denied pain or sensitivity. No erythema or purulence was associated with the exposed bone. Based on his history of bisphosphonate treatment and the duration of exposed bone, the patient was diagnosed with stage 1 ONJ. Because of more pressing medical issues, the patient did not return for follow-up until 3 years later. At that time, necrotic bone was still noted to be present (Fig 4D), as was the carious left maxillary third molar (Fig 3D). The patient was referred to a tertiary care center near his home for treatment and is being closely monitored.

CASE 3

A 57-year-old man with FD/MAS presented for dental clearance before orthopedic surgery. The patient had severe FD involving the lower extremities and pelvis, café-au-lait macules, and renal phosphate wasting. He had a history of multiple pathologic fractures requiring orthopedic surgeries. Eleven years before his current presentation, the patient received a 2-year course of bisphosphonates from 46 to 48 years of age for treatment of FD-related bone pain. He was initially treated with zoledronic acid 6 mg every 6 months for the first year and transitioned to 4 mg every 3 months for the subsequent year.

The patient’s dental care had been sporadic owing to financial issues and dental phobia. Seven months before his current presentation, he underwent a preoperative dental evaluation in preparation for a planned total femur replacement. The general dentist observed carious root tips, generalized caries, and a horizontal partial bony impacted left mandibular first molar (Fig 5A). Ten teeth were recommended for extraction, but the patient elected to limit extraction to the left mandibular first and second molars (ADA teeth 18 and 19) and left mandibular first premolar (ADA tooth 21). After extraction, the patient was prescribed a daily chlorhexidine rinse. At a follow-up evaluation 2 months later, planned restorative work on the right maxillary first molar (ADA tooth 2) and left maxillary first, second, and third molars (ADA teeth 14 to 16) extracted.

At a follow-up evaluation 2 months later, planned restorative work on the right maxillary first molar
and right maxillary first premolar was performed. During the restorative appointment, the dentist noted a cariogenic pulp exposure on the right mandibular first molar (ADA tooth 30), and this tooth was subsequently extracted, as were the left maxillary lateral incisor (ADA tooth 10) and left mandibular first molar (ADA tooth 17; Fig 5B). Two weeks after the extractions, the patient presented to the dental clinic with pain and discomfort because of impacted food in the bilateral extraction sites; the sites were irrigated and the patient was instructed to continue home irrigation. At a follow-up evaluation 3 months later, the intraoral examination showed exposed bone in the lingual mandible bilaterally (3 × 3 mm on the left and 3 × 2 mm on the right side; Figs 6A,B). The patient was asymptomatic and subsequently diagnosed with stage 1 ONJ. The patient was placed on chlorhexidine rinses with close observation.


CASE 4

A 57-year-old woman with FD/MAS presented for routine dental consultation. The patient had polyostotic FD affecting the craniofacial region, ribs, femurs, and tibias (Fig 7A). MAS-related endocrinopathies included precocious puberty and hyperthyroidism after thyroidectomy for poorly differentiated clear cell carcinoma. Because of chronic FD-related bone pain, the patient was prescribed a course of bisphosphonates, which included pamidronate 60 mg every 3 months from 36 to 39 years of age, followed by zoledronic acid 4 mg every 6 months from 39 to 49 years of age.

The patient’s dental history was defined by sporadic dental care, including multiple restorative procedures and extractions. Seven months before presentation, the right maxillary first molar and second premolar (ADA teeth 3 and 4, respectively) were deemed non-restorable and were extracted by the patient’s home providers. At examination at the NIH, a 2-mm non-healing bony defect of the right maxillary alveolar ridge and potential radiographic fistula were noted (Figs 7B, D). Of note, FD was present in the bilateral maxilla, including in the region of the extractions (Fig 7C). The patient was asymptomatic and denied pain or sensitivity and was subsequently diagnosed with stage 1

FIGURE 6. Case 3, intraoral photographs. Photographs were taken 2 weeks after initial presentation of osteonecrosis of the jaw. A, Right posterior mandible with exposed bone along the lingual alveolar ridge (arrow; image is reflected in mirror). B, Patient’s left mandibular lingual alveolus, reflected in mirror. Area of exposed bone is present along the posterior mylohyoid ridge (arrow). Metwally et al. Fibrous Dysplasia and MRONJ. J Oral Maxillofac Surg 2016.
ONJ. The patient reported that her home dentist never mentioned the exposed bone and 1.5 years later reported that the right maxillary wound had healed without complication. Approximately 1 year after her visit to the NIH, the patient also recounted that the left maxillary canine and first premolar (ADA teeth 11 and 12) were extracted because of mobility and marked decay. Three months after this extraction, the patient denied complications, stating that her wounds had completely healed and that a removable partial denture had been fabricated.

**Discussion**

ONJ is an established complication of bisphosphonate use and appears to occur uncommonly in association with FD/MAS. To the authors’ knowledge, these cases are the only reports of bisphosphonate-associated ONJ in patients treated for FD, and cases 1, 2, and 4 are the only reported instances of ONJ occurring in FD bone. In the NIH cohort of 76 patients treated with bisphosphonates, this represents a 5.4% prevalence of bisphosphonate-related ONJ. Although this cohort is not sufficiently large to draw conclusions regarding prevalence in the general FD population, these cases establish that, contrary to previous thinking, patients with FD are at risk for the development of bisphosphonate-related ONJ and should be counseled and monitored accordingly.

The pathophysiology of bisphosphonate-related ONJ in FD and other disorders is not well understood. One proposed mechanism includes inhibition of angiogenesis resulting in an interruption of the vascular supply to the jaws. This is supported by studies showing antiangiogenic properties of bisphosphonates and increasing evidence of a potential association between ONJ and other antiangiogenic agents, such as tyrosine kinase inhibitors and an anti-vascular endothelial growth factor monoclonal antibody. FD bone is highly vascular, and it is unknown whether inhibition of angiogenesis is a contributory factor in the development of ONJ in patients with FD.

Another commonly cited hypothesis links the pathophysiology of bisphosphonate-related ONJ to suppression of osteoclastic bone resorption and remodeling. This could explain the predominant localization of ONJ to the jaws, where intracortical remodeling rates are believed to be increased compared with other skeletal sites, although it should be noted that more recent studies have challenged this paradigm. High bone turnover and increased osteoclastogenesis are characteristic of FD lesions. The effects of bisphosphonates on osteoclast activity within FD lesions have not been fully elucidated; however, 1 study reported no

![FIGURE 7](https://example.com/figure7.png)

**Figure 7.** Case 4, clinical, dental, and intraoral images. A, Technetium-99 bone scan highlighting areas of increased radio-tracer uptake in bone (arrowheads) affected by fibrous dysplasia in the skull, ribs, femur, and tibia. (Fig 7 continued on next page.)

detectable effect on histomorphometric indices, including resorption parameters, in biopsy specimens of patients treated with pamidronate. This is consistent with long-term studies that did not find a consistent effect of bisphosphonate treatment on FD lesion size or radiographic appearance. Therefore, the potential role of suppression of bone remodeling or resorption in the development of these patients’ ONJ is unclear.

Age-related changes in craniofacial FD also might affect the development of ONJ. The natural history of FD lesions is to become established during early childhood, expand during linear growth, and remain relatively quiescent in adulthood. Craniofacial lesions in older patients typically become less homogeneous radiographically, developing discrete radiolucent “cystic”-appearing areas over time. These findings are mirrored histologically, with lesions in older patients showing fewer features characteristic of FD, and in some cases exhibiting normal bone and marrow histology, complete with restoration of hematopoiesis. Decreased vascularity and bone turnover over time might predispose older patients with FD to the development of ONJ. However, the occurrence of ONJ in FD bone in case 2, who presented at the relatively young age of 23 years, argues against this possibility.

The patients presented in this report had multiple features known to be associated with bisphosphonate-related ONJ in the general population. ONJ occurs more commonly in conjunction with nitrogen-containing bisphosphonates, in particular zoledronic acid, as opposed to lower potency non-nitrogen-containing and oral formulations. Higher doses, intravenous formulations, duration of treatment, and more frequent dosing intervals also are correlated with increased risk. All patients described in this report had frequent treatment with zoledronic acid at high doses and over a long period. In addition, all had concomitant periodontal and endodontic infections and underwent dentoalveolar surgical procedures, which also are established risk factors for ONJ. The development of ONJ in these patients likely was the result of a combination of these multiple risk factors.

Current ONJ treatment guidelines stress the need for disease prevention with regular dental examinations and professional prophylaxis before beginning bisphosphonate and non-bisphosphonate antiresorptive or antiangiogenic medication regimens. Periodontal surgical procedures are treated in the same manner as oral and maxillofacial surgical procedures. Evaluation and treatment for MAS-associated endocrinopathies is an essential element of care in patients with FD and should be performed before initiating medical or dental treatments. In active ONJ, treatments can range from debridement of the necrotic bone to aggressive resection of the affected area. Postoperative regrowth is common after conservative debulking and recontouring surgeries in craniofacial FD; therefore, if ONJ is treated surgically, then the FD bone should be monitored to assess response to
surgery. As more patients with FD/MAS are treated with bisphosphonates and antiosteoclastic drugs, it is important to investigate ONJ and other long-term effects of these drugs to develop appropriate treatment and monitoring guidelines.

These cases establish ONJ as a potential complication of bisphosphonate treatment in patients with FD/MAS. The presence of established risk factors for ONJ in this group of patients with FD suggests that high-risk patients could be identified before the development of ONJ. Population studies are needed to identify additional FD-specific risk factors and to determine the prevalence of bisphosphonate-related ONJ in patients with FD/MAS. Future studies investigating the effect of bisphosphonates on histology, turnover, and other morphometric indices could provide insights into the pathophysiology of medication-related ONJ in FD and other conditions. The identification of this potential side effect also highlights the need to be judicious in administering bisphosphonates to patients with FD without a clearly established indication. The current literature does not support a beneficial...
effect of bisphosphonate treatment on FD beyond the treatment of FD-related bone pain. Similar to patients without FD, the development of ONJ can be mitigated by 1) obtaining pretreatment dental screening and initiation of appropriate dental care, 2) using the lowest dose and interval necessary to maintain a therapeutic effect, and 3) using clinical judgment for the use of alternative dosing schedules or drug holidays in patients who require invasive dental procedures.21,41,42

References

FIGURE 7 (cont’d). D, Clinical photograph showing 2-mm bony exposure of the right maxillary alveolar ridge in the area of extraction (arrow). Metwally et al. Fibrous Dysplasia and MRONJ. J Oral Maxillofac Surg 2016.