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Intravenous Bisphosphonate Therapy in the Adult Patient with Osteogenesis Imperfecta: A Literature Review and Case Report

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Osteogenesis Imperfecta (OI) defines a group of genetically varied connective tissue disorders where intravenous bisphosphonate (BP) therapy is common to manage the associated bone fragility. Due to this bone fragility, there is potential for these patients to be regarded as a high-risk group for BP-related osteonecrosis of the jaw (BRONJ). First documentation of BRONJ was in 2003; however few reports discuss the risk of BRONJ relative to BP therapy in patients with OI. Of these reported cases of BRONJ, all have been recorded in patients sixty years and over. As yet, no literature is available to show if OI in adults increases the risk of BRONJ. In this case, a 59-year-old male, receiving intravenous BP therapy for OI, underwent multiple dental extractions under local anesthesia. At subsequent review appointments, no clinical signs of BRONJ were detected.

Keywords: Osteogenesis imperfect; bisphosphonates; BRONJ; oral surgery.

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1. INTRODUCTION

OI, also known as 'brittle bone disease' is a dominant autosomal genetic disorder, with an incidence of 6–20 per 100,000 newborns [1-7]. Since 1998, the use of BPs in patients with OI has shown to increase their bone density and reduce the incidence of bone fractures [2]. While this outcome is ideal, therein lies the risk of BRONJ. This risk correlates with duration of exposure and therefore cumulative dose. It is also associated with dental interventions, medical co-morbidities or, on occasion, with no identifiable aggravating factor [2,8,9]. The risk of BRONJ has caused great concern when these patients require dental extractions. Only a few reports discuss the risk of BRONJ in patients with OI [8-11]. Of these reported cases, all have been recorded in subjects in OI patients older than 60 years of age [5].

In patients with OI, long bone fractures are frequently observed due to synthesis defects in type I collagen [10-13]. Dentinogenesis imperfecta (DI), a disturbance in the development of the permanent dentition may also be associated with this collagen defect [12,14].

The features of OI are classified into types I–IV based on typical characteristics. Three uncommon groups were later added: types V–VII. Types I–IV involve mutations in the genes COL1A and 1B. Types V–VII lack the severity of this gene mutation. Type I is a mild form of OI, type II is severe and prenatally lethal, type III is deforming and type IV is mildly deforming (Table 1) [13-15].

OI may be accompanied by DI and thus, craniofacial and oral manifestations may be observed concomitantly [15]. These can be of significance if the overt physical signs of OI are not evident, and the diagnosis is uncertain. DI affected dentition exhibit an opalescent greyish-brown hue. The enamel may be of normal thickness, however commonly is dislodged to expose the dentin. This enamel dislodgement may be attributed to the smooth dentinoenamel junction, which is scalloped in unaffected healthy teeth (Table 2) [15]. Furthermore, this smooth junction increases susceptibility to breakdown and decay.

Medical treatment of OI can typically include prescription of calcitonin, sodium fluoride, growth hormones, cortisone, anabolic steroids, vitamins C and D, minerals and BPs [15]. The most effective treatment is BP therapy, which results in minimization of osteoclast activity [13]. BPs were originally developed for the treatment of bone-resorbing diseases such as multiple myeloma and bone metastasis, the classic origins of which are breast and prostate cancer, and tumour-related hypercalcemia. More recently, patients with osteoporosis and Paget's disease have been using BPs to reduce the risk of pathological fractures and related morbidities [3].

BPs are comprised of a pyrophosphate-like structure, whose hydroxyl group confers a strong affinity to hydroxyapatite. The half-life in humans is approximately eight to ten years due to deposition and storage in bones. Concentration of BP deposits occur in areas of high rate bone turnover with accumulation of osteoclasts [3]. Nitrogen-containing BPs (nBP) are more potent in the inhibition of mineral dissolution, mevalonate pathway, apoptosis and subsequent inhibition of osteoclast activity. As a result, nBPs induce a greater risk and incidence of BRONJ than non- nitrogenated BPs [3].

Table 1. Classification of OI

Type	Characteristics
I	Mild form, normal stature, minimal or no deformity, fragile bone, blue sclera, hearing losses, autosomal dominant and recessive inheritance
II	Severe and perinatally lethal type, poor cranial mineralization, fragile bone and severe long bone deformity, autosomal dominant inheritance
III	Deforming type, fragile bone and long bone deformities, short stature, sclera variable in colour, dentinogenesis imperfecta and hearing losses common, autosomal dominant and recessive inheritance
IV	Mildly deforming, variable short stature, fragile bone, normal sclera, dentinogenesis imperfecta common, hearing loss variable, autosomal dominant inheritance

Table 2. Genetically conditioned dysplasias of dentin

DI type 1	Displays manifestations of OI
DI type 2	No manifestations of OI
DI type 3	Brandywine type showing shell teeth

The rates of BRONJ are very low. The risk of developing BRONJ on IV and oral BP is 0.8-12% and 0.0007% respectively. Risk factors for BRONJ include a history of trauma, dental surgery or dental infection and intravenous BP administration. In addition, age and duration of BP therapy increase BRONJ risk [5-7]. Although a direct causal relationship with BPs cannot be assumed, these agents may possibly contribute to the development of BRONJ by suppression of bone remodeling in the jaw [3,6].

Management of OI involves symptom management intended to encourage normal function [14]. Physical therapy improves both muscle strength and functional strength [13]. Surgical interventions include correcting or reducing deformities, and orthopaedic stabilization of the long bones and spine to avoid recurring fractures [13]. Facial malformation and malocclusion, including retrognathic maxilla and a prognathic mandible, can be corrected by orthodontic and maxillofacial surgical interventions [13,14]. Odontological interventions for oral health are mainly preventive measures for caries and periodontal risks. While orthognathic surgery in patients with OI is uncommon due to increased risk of complications, most cases result in a successful outcome with stable occlusion [15].

2. REPORT OF CASE

A 59 year-old male presented to the State Dental Clinic, the Oral Health Centre of Western Australia, and his chief complaint was regarding his of severely broken down maxillary dentition (Fig. 1). The patient reported a gradual degeneration of his dentition over many years despite attempts to maintain a good oral hygiene regimen.

The patient's medical history revealed OI type I, diagnosed as a young child. The prescription medications that patient was on included the BP zolendronic acid, administered as an annual 5 mg intravenous dose for three years in conjunction with a combined calcium and vitamin D supplement. The patient experiences chronic fatigue secondary to hypothyroidism. The patient had a surgically repaired fractured mandible, with no associated healing complications as he can recall. The mandibular fracture was satisfactorily repaired with fixation wire, as seen in Fig. 1. The patient has two children with the eldest child also diagnosed with OI type I.

Upon examination, the patient was frail, with small stature, thin build, triangular face and blue sclera (Fig. 2). Intra-orally, the maxillary dentition exhibited numerous severe carious lesions, multiple decoronated teeth and retained carious root fragments (Fig. 1).

Several treatment options were discussed with the patient until a definitive treatment plan was developed. Alternative treatment options included extraction of retained root stumps and temporary restorations of carious teeth, or extraction of retained root stumps, decoronate and root canal treat carious teeth with the aim to fabricate overdentures, or dental clearance and fabricate complete maxillary and mandibular dentures. As part of treatment planning, the case was discussed with an oral surgeon and endodontist. After discussing the pros and cons of each treatment option, the patient consented for dental treatment as outlined in the definitive treatment plan. The dental treatment plan involved extraction of all maxillary dentition, both right mandibular premolar teeth and right first molar root fragment performed under local anaesthesia after consultation with an oral surgeon. Endodontic treatment of the mandibular incisors was completed and remaining mandibular carious lesions were restored using glass-ionomer cement. Post-operative recovery and healing was satisfactory at regular follow-up appointments, and fabrication of a complete maxillary denture commenced after satisfactory healing was observed for six months.

3. DISCUSSION

In patients with OI, all connective tissue is affected. Collagen is the most prevalent protein in the body and is an element of bone, teeth, cartilage and blood vessels. There are nineteen types of collagen and the most common form, collagen type 1, primarily provides mechanical strength. OI arises as a result of mutations in the genes COL1A and 1B [12-14].

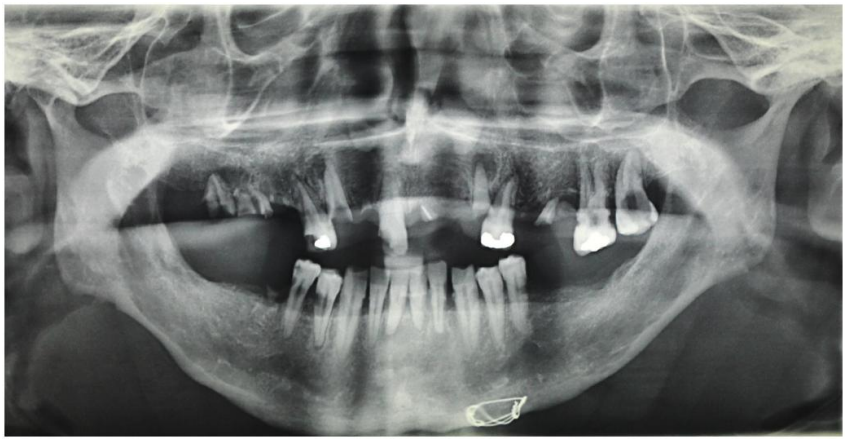

Fig. 1. Orthopantogram showing dentition and fixation wiring for mandible fracture

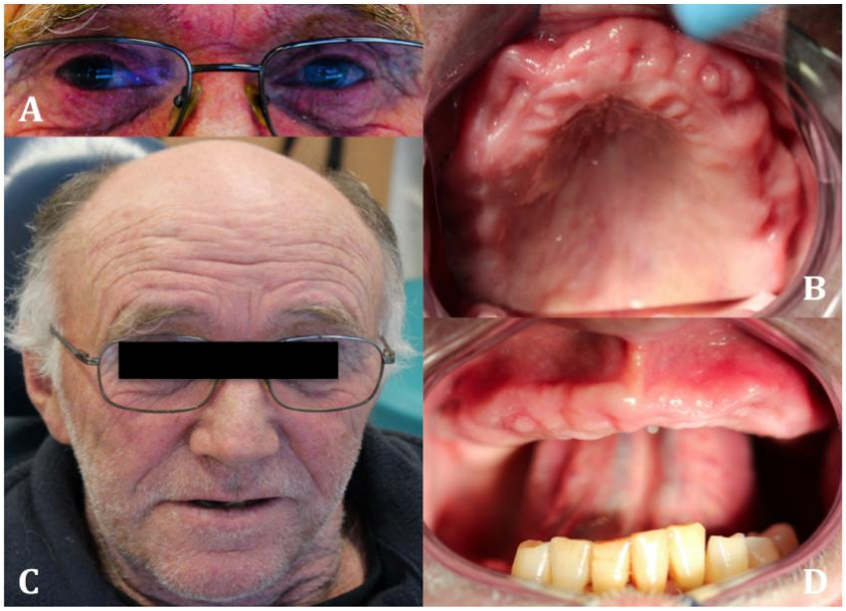

Fig. 2. A – Grey blue Sclera, B – Portrait showing triangular shape, C and D – Healed tissues of maxilla with no clinical signs of BRONJ

With escalating incidence of BRONJ, the use of BPs should be cautiously considered in patients at risk. Suitable preventive measures need to be implemented, which can include regular dental reviews, emphasis on oral hygiene, prophylactic extractions and calculated prescription of BPs. It is important that medical and dental teams work together to minimise dental afflictions whilst utilising BPs in the treatment of patients with OI to their full potential [9-14].

4. CONCLUSION

The rates of BRONJ in patients on BPs are low. However, traumatic events such as dental extractions increase the risk of BRONJ, specifically with the administration of IV BPs, illustrates the importance of regular dental check ups. Preventative measures will reduce the need for invasive procedures such as dental extractions, which increases the risk of patient's taking BPs developing BRONJ. Understanding the risks associated with BRONJ, dentists should manage patients as conservatively as possible. However, if patients do require invasive treatments such as dental extractions, it would beneficial to take a multidisciplinary approach to ensure the best outcome for the patient.

CONSENT

Informed consent was obtained for this patient for case report.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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