IN BRIEF

- Bisphosphonates are a class of drugs that reduce the rate of bone turnover.
 - Osteonecrosis is a drug-induced condition in which part of the jawbone dies and cannot regenerate due to lack of blood supply.
 - Oral manifestations of drug actions and side effects are well known.
- This paper outlines guidelines for management.

Bisphosphonate induced osteonecrosis of the jaw mimicking a tumour

M. Pancholi,¹ A. Edwards² and S. Langton³

Osteonecrosis has been well-documented in the past. We present an example of this complication that we recently saw in our department which on initial presentation appeared to be squamous cell carcinoma. This case is particularly important as the condition will become more and more prevalent and therefore it is imperative that GPs in primary care are aware of it.

INTRODUCTION

Bisphosphonates are widely used in the management of metastatic disease to the bone, Paget's disease and in the treatment of osteoporosis.¹ They are capable of localising to bone and have a strong affinity with osteoclasts, inhibiting their function.² Bisphosphonates bind to exposed bone mineral around resorbing osteoclasts and thus disturb osteoclast-mediated bone resorption, and decrease bone turnover. At a cellular level, the drugs inhibit the recruitment of osteoclasts and initiate apoptosis at the bone surface, including reducing the life-span. This may possibly be due to stimulation of osteoclast inhibitory factor, prevention of osteoclast development from bone marrow precursors, and down regulation of matrix metalloproteinases.²⁻⁶ It is thought that bisphosphonates modulate osteoclast function by interacting with cell surface receptor or an intracellular enzyme.¹

Despite uncertainty regarding the exact method of action of bisphosphonates, their role in decreasing osteoclast-mediated lysis of bone has been well established in clinical trials. They have been shown to reduce skeletal tumour load in patients with multiple myeloma, breast cancer and prostate cancer.⁵ It has recently been reported that bisphosphonates are capable of causing osteonecrosis of the jaws.^{1,3,5-7} It is seen predominantly in intravenously-administered bisphosphonates, mainly pamidronate (Aredia) and zoledronate (Zometa), indicated for the management of hypercalcaemia of malignancy. However, it has also been reported in patients taking oral bisphosphonates, alendronate (Fosamax) and risedronate (Actonel), used in the management of osteoporosis and Paget's disease. Pamidronate and zoledronate are nitrogen-containing bisphosphonates, are much more potent and are not metabolised. Therefore they accumulate in bone and have an ongoing effect that results in bone necrosis.^{1,3-4} Ibandronate is a single-nitrogen bisphosphonate, available in IV or oral formulations, with similar efficacy for treatment of metastatic bone disease.

The other main risk factors for osteonecrosis of the jaw are invasive

dental procedures and poor oral hygiene, corticosteroid therapy and radiation therapy.⁹

We describe a case of osteonecrosis of the maxilla associated with long-term bisphosphonate therapy for metastatic breast cancer.

CASE REPORT

A 51-year-old female was referred initially by the Specialist Registrar in clinical oncology regarding problems with her dentition, mainly brittle teeth and halitosis. She was subsequently referred to the Multi-Disciplinary Head and Neck team regarding a suspicious lesion in the upper right maxilla (Fig. 1).

Her past medical history included breast cancer for which she underwent a wide local excision and axillary clearance in October 2000. A six cycle chemotherapy regime was given over three months which included: cyclophosphamide, methotrexate and 5-fluorouracil. Isotope bone scan confirmed skeletal metastasis in the left shoulder where an isolated fraction of radiotherapy was given. She commenced oral Clodronate (bisphosphonate therapy) in April 2001. Eleven monthly cycles of IV Pamidronate were commenced in January 2002 after stopping her oral bisphosphonate

¹Senior House Officer in OMFS, ²Specialist Registrar in OMFS, ³Consultant Oral and Maxillofacial Surgeon, Royal Blackburn Hospital, Haslingden Road, Blackburn, BB2 3HH
Correspondence to: Dr Menal Pancholi
Email: mpancholi@talk21.com

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drug due to development of further bony metastasis. She then recommenced monthly IV therapy in the form of Zolendronic Acid in December 2002. The patient recommenced oral therapy in the form of Ibandronic acid in August 2004. She stopped her bisphosphonate therapy after her oral diagnosis was made.

At the time of presentation, the patient reported pain and swelling in the cheek, problems with blowing her nose on the right hand side, weight loss and also bad breath.

On examination, there was: marked halitosis, extensive dental caries in her lower dentition, and a large bony defect in the upper right quadrant of the maxilla mainly involving the buccal alveolus. This lesion seemed highly suspicious of carcinoma, either a primary of the oral mucosa or a secondary metastasis from her primary breast cancer.

Initial radiographic examination with an occipitomental facial view (Fig. 2) showed non-specific features (radiopacity of the right maxillary antrum) and did not highlight the magnitude of the lesion.

An urgent biopsy under local anaesthesia was carried out with two specimens taken: one of a segment of bone from the right maxilla and the other palatal mucosa adjacent to the necrotic bone.

The pathology report indicated fragments of bone showing osteonecrosis with no evidence of metastasis. The palatal mucosa showed only inflammation with no evidence of ulceration or neoplasia. On review, the patient had a marked fenestrated/sequestered area in the right maxilla which has all the features of neoplasia.

As a result, the patient underwent further exploration and biopsy of both bone and soft tissue of the right maxilla under general anaesthesia. Examination and exploration revealed an extensive area of necrotic bone and soft tissue in the maxilla.

The histopathology report showed moderate to severe, acute and chronic inflammation with extensive mucosal ulceration. This included colonies of actinomyces organisms. Again there was no evidence of dysplasia or malignancy in the biopsy sections. A diagnosis of osteonecrosis of the maxilla associated with the use of bisphosphonates was therefore made.

Fig. 1 Photograph showing extensive bone destruction in the upper right maxilla

Fig. 2 Occipitomental radiograph showing radiopacity of the right antral region

Initial treatment and management included removal of sequestered areas of necrotic bone on three occasions. Long term antibiotic therapy was commenced to deal with any superadded infection – 150 mg clindamycin being the drug of choice. Her analgesic requirements were addressed requiring the use of opioid and non-opioid medication. She is at present stable with no further bony destruction apparent.

In addition to the regime instigated for her presenting condition a full oral assessment was carried out to address the needs of her oral hygiene and condition of her remaining dentition. A treatment plan was prescribed in consultation with our restorative colleagues to facilitate rehabilitation of soft and hard tissues.

As indicated she had suffered a degree of weight loss because of her reduced dietary intake due to both pain and functional impairment. Her nutritional status was assessed and appropriate supplementation provided after input from our dietician within the multi-disciplinary team environment.

A reconstructive option is planned with a prosthesis to obturate the defect in the first instance.

DISCUSSION

Bisphosphonate-mediated inhibition of osteoclast function seems to decrease bone resorption and inhibit normal bone turnover remodelling. Bone resorption and remodelling play an essential role in maintaining normal bone

homeostasis. As osteoclasts occurs, cytokines and growth factors are released into surrounding matrix essential for modulating new bone development.^{1,5}

However, bisphosphonates may alter bone homeostasis sufficiently that the ability of bone to heal after minor insults is compromised. The bone may also become secondarily infected and sequester, leading to a lesion that appears clinically similar to osteoradionecrosis.^{3,10}

Pathogenesis of the osteonecrotic process is most consistent with localised vascular insufficiency. This is believed to be important in reducing tumour burden by depriving tumour cells of adequate nutrients and blood supply. However, if osteoclastic function is too severely impaired, osteocytes are not replaced and the capillary network in the bone is not maintained, resulting in avascular bone necrosis.^{3,5,10}

A retrospective review of 63 patients who presented with refractory osteomyelitis and history of chronic bisphosphonate therapy was performed. Fifty-six patients had received IV bisphosphonates for various malignant diseases (seven for osteoporosis). The presenting lesions were either non-healing extraction socket or an exposed jawbone—both being refractory to conservative debridement and antibiotic therapy.¹ This is supported by a study of 36 patients with painful bone exposures in the jaws that were unresponsive to surgical or medical treatments.⁴ Another report describes 17 patients with cancer with bone metastases who subsequently developed osteonecrosis of the jaws.⁷ Spontaneous exposure of bone may be due to thinness of the oral mucosa, with the mandibular lingual plate, tori, the mylohyoid ridge and the internal oblique ridge frequently involved in osteonecrosis.

Ibandronate-associated osteochemonecrosis of the jaw seems to be a rare adverse effect due to the small number of cases (seven). It was observed only in patients being treated for metastatic bone disease, but the association was confounded by prior treatment with an alternative bisphosphonate.¹⁰

In this particular case the patient had over a five-year period received a combination of both IV bisphosphonate therapy and oral therapy which may well have made her at high risk of developing the condition. Concomitant medication during these five years includes chemotherapy agents as mentioned previously as well as hormone antagonists Tamoxifen, Exemestane and Anastrozole. This poses the question of synergistic activity with bisphosphonates.

At present, there is no effective treatment for the condition. Surgical intervention tends to expose further bone and locating viable bone margins is problematic. Covering exposed bone with tissue flaps is ineffective because of development of fistulae around the flaps.^{1,5} Because osteonecrosis and its complications can result in significant chronic pain, dysfunction and disfigurement which are difficult to treat, the aim should be prevention.²

Dental surgery seems to be a precipitating event in development of most cases of bisphosphonates-related osteochemonecrosis.⁴ It is therefore imperative that patients receiving necessary treatment have their dental status assessed prior to bisphosphonate therapy. This includes control of dental caries and periodontal disease, avoiding dental implant placement, using soft liners on dentures, and to recommend an alternative to tooth extractions for patients with history of receiving bisphosphonate therapy.⁴⁻⁷ This is because

withdrawal of bisphosphonate therapy before major dental procedures does not appear to hasten recovery of osteonecrosis due to their persistence in bone.³

In established cases, the primary goals are palliation and control of osteomyelitis. Progression of disease usually controlled with antibiotics and periodic surgical debridement of sequestering bone and wound irrigation.⁵ However, these have proven consistently ineffective.² Surgical treatment should only be reserved for symptomatic patients.

It is important to make health care professionals and patients aware of the potential risk. There should be greater collaboration between medical oncologists, oral and maxillofacial surgeons and dentists.

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