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Osteonecrosis of the jaws associated with the use of zoledronic acid in multiple myeloma patients

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Osteonecrosis of the jaws has recently been identified as a complication in patients treated with bisphosphonates. We report two case-reports of patients with multiple myeloma treated with zoledronic acid who had developed osteonecrosis of the mandible. The duration of treatment with zoledronic acid was 13 months in each case, with a cumulative zoledronic acid dose of 72 mg in one case and 144 mg in the other. The lesions were resistant to conservative debridement, surgery and antibiotic therapy. Clinicians should be aware of this potential serious complication i.e. bone necrosis in multiple myeloma patients receiving long-term treatment with potent bisphosphonates. It is recommended to perform dental examination to identify and treat all predisposing conditions before bisphosphonate treatment is started.

Key words: osteonecrosis, bisphosphonates, zoledronic acid, multiple myeloma

Introduction

The use of bisphosphonates combined with antineoplastic chemotherapeutic agents is considered a standard in the treatment of hypercalcemia associated with malignancy and of metastatic osteolytic lesions associated with breast cancer and multiple myeloma [1, 2]. More recently, the indications for bisphosphonate treatment have been extended to osteolytic lesions caused by any solid tumor. This has resulted in a rapid increase of consumption of bisphosphonates in the majority of medical oncology practices within the past several years. Pamidronate and zoledronic acid are licensed for use in multiple myeloma with bone lesions. However, they are widely applied off label in patients without bone lesions, and often in smoldering disease.

Jaw osteonecrosis has recently been identified as a complication in bisphosphonate–treated patients [3-7]. Ruggiero et al [8] have performed a retrospective chart review of patients who presented to their Oral Surgery service between February 2001 and November 2003 with the diagnosis of refractory osteomyelitis and a history of chronic bisphosphonate therapy. Sixty three patients have been identified with such a diagnosis. Fifty-six patients had received intravenous bisphosphonates (pamidronate 34, zoledronic acid 9, pamidronate and zoledronic acid 13) for at least 1 year. The most common oncologic diagnoses at presentation were multiple myeloma (28 patients) and breast cancer (20 patients), followed by prostate cancer (3 patients), lung cancer (1 patient), uterine leiomyosarcoma (1 patient), plasmocytoma (1 patient) and leukemia (1 patient). Seven patients with a diagnosis of osteoporosis were on chronic oral alendronate (6 patients) and risedronate (1 patient) therapy and had no history of malignant disease or chemotherapy exposure. The typical presenting lesions were either a nonhealing extraction socket or an exposed jawbone; both were resistant to conservative debridement and antibiotic therapy. Biopsy of these lesions has shown no evidence of metastatic disease. A majority of these patients required surgical procedures to remove the involved bone.

In a study of Singhal et al [9] 15 cases of jaw osteonecrosis were identified among 650 myeloma patients (incidence 2.5%) seen between March 2001 and August 2004. All patients were on pamidronate (4 patients) or zoledronic acid (11 patients) at standard doses when osteonecrosis was diagnosed. The duration of bisphosphonate therapy prior to the development of symptoms ranged from 4 to 75 months (median 50). The outstanding symptom was local pain and discomfort, and bone protrusion within the oral cavity.

Thakkar et al [10] have reported 16 cases of multiple myeloma treated with bisphosphonates in which patients had developed periodontitis/osteomyelitis of the jaw. All were treated with bisphosphonates for an average of 8 months (range 4-17 months) prior to the onset of new jaw symptoms. Six patients were receiving zoledronic acid and 10 – pamidronate.

Woo et al. have seen more than 20 cases of osteonecrosis of the jaw in patients with myeloma at their

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institution over a period of six months, although they had observed very few such cases in previous years [11].

In a study of Maerevoet et al [12], 9 cases of biopsy-proven osteonecrosis of the jaw were diagnosed at their institution between December 2003 and July 2004 (4 in patients with multiple myeloma and 5 in patients with metastatic breast cancer) among 194 patients treated with zoledronic acid (4.6%). Before receiving zoledronic acid, 6 of those 9 patients had been treated first with pamidronate (90 mg every three or four weeks). The median duration of treatment with pamidronate was 39 months (range, 4 to 58). For zoledronic acid, the median duration of therapy before the appearance of osteonecrosis was 18 months (range, 4 to 22), and the median cumulative dose was 72 mg (range, 36 to 88).

In 2004, the International Myeloma Foundation conducted a Web-based survey to assess the risk factors for osteonecrosis of the jaw. Of 1203 respondents, 904 had myeloma and 299 breast cancer. Both osteonecrosis and suspicious findings, including bone erosions and spurs plus exposed bone were assessed. Sixty-two patients with myeloma had osteonecrosis of the jaw and 54 had suspicious findings; 13 patients with breast cancer had osteonecrosis and 23 had suspicious findings – a total of 152 patients with either osteonecrosis or suspicious findings. It was found that osteonecrosis of the jaws was most strongly associated with use of pamidronate and/or zoledronic acid. Of the patients with myeloma, 71% had received zoledronic acid and 29% had received only pamidronate. This risk was time – dependent and became significant at 12 months, increasing thereafter to 36 months. With data censored at 36 months, the estimated incidence of osteonecrosis among patients receiving zoledronic acid was 10% and that among those receiving pamidronate was 4% [13, 14].

The aim of the paper is to present two cases of multiple myeloma who had developed jaw and dental complications most likely associated with the administration of a third generation bisphosphonate – zoledronic acid. These complications have already drawn our attention earlier [3].

Case reports

Case 1

A 56-year – old man was diagnosed with multiple myeloma in 1998 on the base of plasma cells in the bone marrow increased up to 56%, generalised osteolysis and the presence of monoclonal protein IgGκ in the serum. Apart from anti-myeloma therapy initially performed with melphalan, and continued until the present (September 2005) with chemotherapy according to the VMCP/VBAP regimen, between 1999 and 2000 the patient had also been treated with zoledronic acid. This bisphosphonate was systematically administered every month as an intravenous infusion in a single dose of 8 mg. Altogether 18 cycles were administered. In 2000 the patient had also been irradiated to the spinal cord.

In 1999 it became necessary to remove the majority of his carietic teeth and roots. The patient's alveolus healed. During a number of months after the installation of denture he developed a wound in the gum from which the protruding bone occasionally found to be crumbling. During two subsequent years the alveolar part of the lower jaw bone remained uncovered. An X–ray survey of the mandible revealed destruction of bone texture with a tendency to a form of sequestration of the destroyed bone (Figure 1). Biopsy of these lesions provided no evidence of malignancy. Bone destruction progressed.

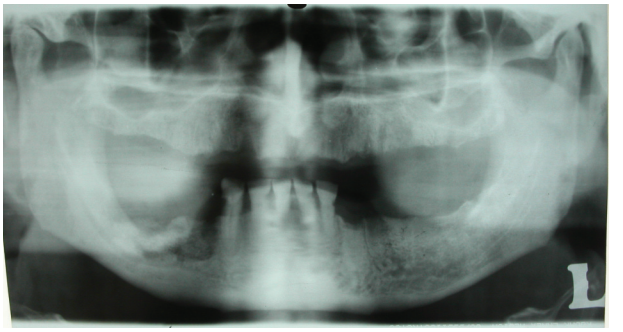

Figure 1. Mandible osteonecrosis in a patient treated with zoledronic acid 8 mg monthly

In 2004 osteolytic changes appeared and the body of the mandible fractured (Figure 2) opening a mandibular fistula. Cultures from the mandibular lesions revealed the changing presence of different bacteria: *Staphylococcus epidermidis, Streptococcus salivarius ssp.salivarius, Morganella morgani, Prevotella intermedia/disiens, Prevotella oris buccae, Escherichia coli* and anaerobic Gram-negative species. The treatment of mandibular

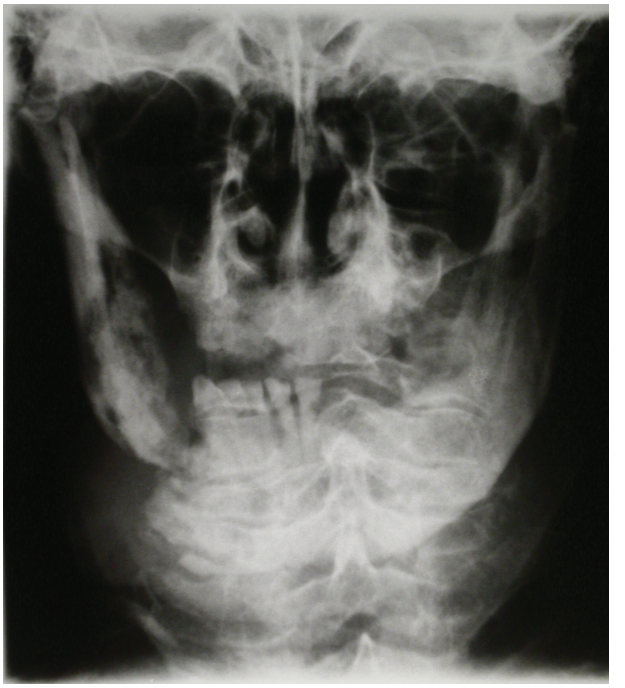

Figure 2. Mandible of the patient treated with zoledronic acid 8 mg monthly three years later. The body of the mandible fractured and osteolytic lesions occurred

lesions included antibiotic administration according toculture results, sequestrectomy of the bone in the alveolar part of the mandible to the right side of teeth 47 and 46 (October 2002), and later, after the development of osteolytic lesions, irradiation to the mandible. At present, 61 months after the end of zoledronic acid administration non healing lesions in the oral cavity continue to remain a serious therapeutic problem.

Case 2

A 55 – year – old patient with multiple myeloma diagnosed basing upon bone marrow plasma cell rate increased up to 29%, skull and rib osteolysis and the presence of M-protein IgAλ in the serum. VMCP/VBAP treatment led into remission in 1999. Apart from chemotherapy during the years 1999-2000 the patient had been administered zoledronic acid in a dose of 4 mg as intravenous infusions every month altogether amounting to 18 cycles. In 2000 it was necessary to perform to extract carietic teeth and prepare dentures. After just over a year the patient developed painful bone exposure in the alveolar part of the mandible. No osteolytic changes were found within the jaws (Figure 3). This lesion proved resistant to any form of dental treatment, including surgical removal of necrotic tissue and administration of numerous antibiotics according to the results of cultures obtained from the lesion. The lesion persisted until the patient's death among symptoms of pancytopenia and sepsis 27 months after completing zoledronic acid administration and 47 months after the diagnosis of multiple myeloma.

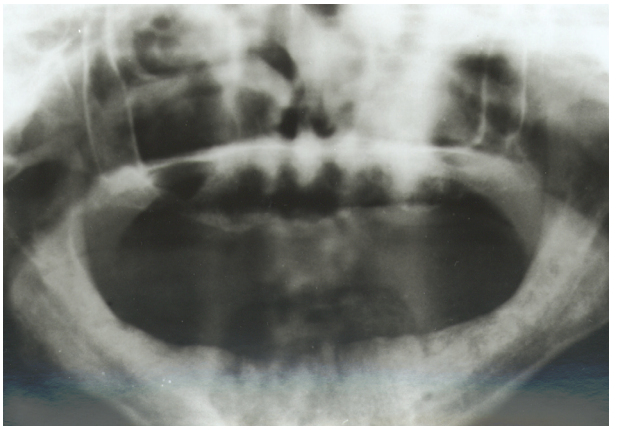

Figure 3. Mandible lesions in a patient treated with zoledronic acid 4 mg monthly

Discussion

Bisphosphonates are powerful osteoclast inhibitors with antiangiogenic properties and a half-life of many years (15). The potent bisphosphonate-mediated inhibition of osteoclast function decreases bone resorption and inhibits normal bone turnover remodeling, thus resulting in microdamage accumulation and reduction of some mechanical properties of bone [16-19). The mandible and maxilla are generally bisphosphonate-seeking bones, as evidenced by scintigraphy revealing increased bone turnover with repetitive chewing motion. The role of bisphosphonates in perpetuating infection is probably multi-factorial. Angiogenesis inhibition may be involved, as well as the prevention of debris clearance by osteoclasts [20-22]. Also in myeloma the immune system tends to become compromised, thus developing a fertile medium for infection and further destruction. Additionally, in an acidic environment, such as that potentially resulting from infection, bisphosphonates are more rapidly released from bone hydroxyapatites into the surrounding tissues and are cytotoxic to the local stromal cells. As the nitrogen containing bisphosphonates are rapidly released, they may up-regulate the inflammatory response by stimulating IL-1 and IL-6. As more inflammation ensues there is more release of bisphosphonates. This continuous cycle perpetuates an unstable local environment [4, 8, 10].

The pathogenesis of the osteonecrotic process is rather consistent with localized vascular insufficiency [4-6, 8, 23]. Osteonecrosis of the jaw probably results from the inability of the hypodynamic and hypovascular bone to meet the increased demand for repair and remodeling owing to physiologic stress (mastication), iatrogenic trauma (tooth extraction or denture injury), or tooth infection in an environment that is trauma-intense and bacteria–laden. Coexisting factors may include the use of other medications with antiangiogenic properties, such as glucocorticoids, thalidomide, and bortezomib in patients with myeloma and other factors, such as diabetes mellitus, irradiation of the jawbone, peripheral vascular disease and hyperviscosity syndrome [11].

The management of patients with bisphosphonate-related osteonecrosis is difficult, as we have also shown in the case reports. Radical resection appears to be of limited use in cases of osteonecrosis of the jaw and may be contraindicated; the disease may progress despite surgery and cessation of bisphosphonate therapy [8].

The efficacy and safety of clodronate (24), pamidronate (25) and zoledronic acid (3) in the treatment of myeloma bone disease have been evaluated in a prospective study performed at our institution. In none of the cases treated with clodronate or pamidronate did we observe osteonecrosis of the jaws. However, in our study we had aministered pamidronate in a dose of 60 mg, intravenously, every month, and not in a dose of 90mg as it had been used by other authors who had reported the occurrence of jaw osteonecrosis in patients receiving pamidronate [9, 10, 12]. In our studies osteonecrosis of the jaws developed in 2 out of 6 patients treated with zoledronic acid [3]. Literature data also proves that osteonecrosis of the jaws has been most commonly observed in patients receiving zoledronic acid [7, 9, 12, 14].

Finally, it is worth to note that clinicians should be aware of the possibility of implant failure and delayed wound healing, especially in patients receiving intravenous bisphosphonates for malignant tumors. Dental implant failures attributable to oral bisphosphonate therapy have been reported in patients with osteoporosis [26, 27].

Conclusions

Bisphosphonate use can be associated with jaw or dental problems, including pain, bone necrosis and poor healing. These problems are more likely to occur after longer periods of bisphosphonate use and after the application of more potent bisphosphonates e.g. zoledronic acid. The risk is increased by major dental procedures and poor dental hygiene. Early diagnosis might prevent or reduce the morbidity resulting from destructive lesions of the jaw bones. Complete dental evaluation and treatment should be performed prior to the onset of bisphosphonate therapy. Once bisphosphonate therapy has begun, dental extractions, placement of dental implants and any other interventions must be undertaken with due caution. Major surgical interventions should be avoided. It is recommended to withdraw bisphosphonates for a period of at least 3 months prior to invasive dental procedures to allow for the recovering of osteoclastic activity, removing debris and reducing the chance of creating a fertile bacterial medium. In patients with multiple myeloma on bisphosphonate therapy who report dental/jaw discomfort a careful examination (including jaw imaging in case of any local symptoms) should be performed to exclude infectious etiology. Patients receiving bisphosphonates who have developed dental infections, should be taken of biphosphonate therapy until the infection is controlled. In patients developing jaw osteonecrosis, not only bisphosphonates, but also potential co-factors or co-triggering factors should be stopped or avoided. If it is at all feasible, steroids such as prednisone or dexamethasone should be discontinued or reduced. There should be no irradiation therapy involving the head and neck. It is very important to carefully assess the need for bisphosphonate therapy and to avoid their administration in plasma cell dyscrasias, where their usefulness has not been established yet (e.g. smoldering myeloma). One should also remember that with the extension of treatment duration the effect of bisphosphonates on skeletal morbidity becomes less pronounced [25, 28].

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