Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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Denosumab osteonecrosis of the mandible: a new entity? A case report.

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ABSTRACT

In the treatment of osteoporosis, M. Kahler and bone metastases from prostate and breast cancer bisphosphonates play a major role. Not all patients respond well to bisphosphonate treatment. Since a few years adverse effects of these drugs have been reported. A new drug, denosumab, a fully human monoclonal antibody to RANKL, has recently been developed. This case reports a 74-year-old male patient with a medical history of diabetes mellitus, angina pectoris, coronary bypasses, hypertension, and prostate cancer with multiple metastases to lymph nodes, bone and lungs. The prostate cancer was treated according to the protocol. But he was never treated with bisphosphonates. Instead he was included in a phase III randomized double blind multicenter trial, testing the efficacy of denosumab compared to zoledronic acid in the treatment of bone metastases of hormone resistant prostate cancer. Only 7 months after start of denosumab infectious symptoms developed, followed by infestation of the mandible. Despite surgical treatment fistula and exposed bone remained. This case illustrates that use of denosumab can lead to a type of osteonecrosis resembling bisphosphonate related osteonecrosis of the jaws.

INTRODUCTION

In the treatment of osteoporosis multiple myeloma and bone metastases from prostate and breast cancer bisphosphonates play a major role. Bisphosphonates, particularly the use of intravenous bisphosphonates, reduce bone resorption by inhibiting osteoclast function, thereby reducing pain[1,2] and correcting hypercalcemia[3,4]. However, not all patients respond well to bisphosphonate treatment and even in those who do respond well, there is increasing awareness and reporting of the adverse effects of these drugs in the literature[5]. Many of these reports relate to concerns regarding gastrointestinal complaints, but more frequently 0,01%-9,1% osteonecrosis of the jaw is being recognised and reported[6]. This is a serious condition which can lead to loss of part if not all of the jaw even in the face of best known treatment. Intravenous use of bisphosphonates are limited in dosage because of their renal toxicity[7]. In addition bisphosphonates have a long half-life and once incorporated into the bone, remains effective for several years after intake. In the search for a better solution a new drug, Denosumab (Prolia, Xgeva: Amgen Europe), a fully human monoclonal antibody targeted to Receptor Activator of Nuclear Factor kB Ligand (RANKL), has recently been developed. RANKL has been found to act as the primary signal for bone removal[8-16]. Denosumab is more effective in inhibiting osteoclasts in comparison to bisphosphonates. Because there is no binding to bone, it potentially will reduce the long term effects associated with bone incorporation. Denosumab's binding to RANKL theoretically will produce a more physiologic action with hence fewer side effects. Its main indications for use are stated to be osteoporosis and bone metastases with the drug having recently been granted approval by the FDA for these indications.

There have been several publications on Denosumab, most reports investigate the effect of denosumab when compared to the effect of bisphosphonates. To our knowledge adverse effects of denosumab on the mandible or maxilla have received relatively little attention[12,17,18]. Osteonecrosis of the jaw may still be one of these adverse effects of denosumab, with the incidence of osteonecrosis of the jaw ranging from 0.9% to 5%[12,14,16].

We present a case of osteonecrosis of the jaw following denosumab treatment.

CASE REPORT

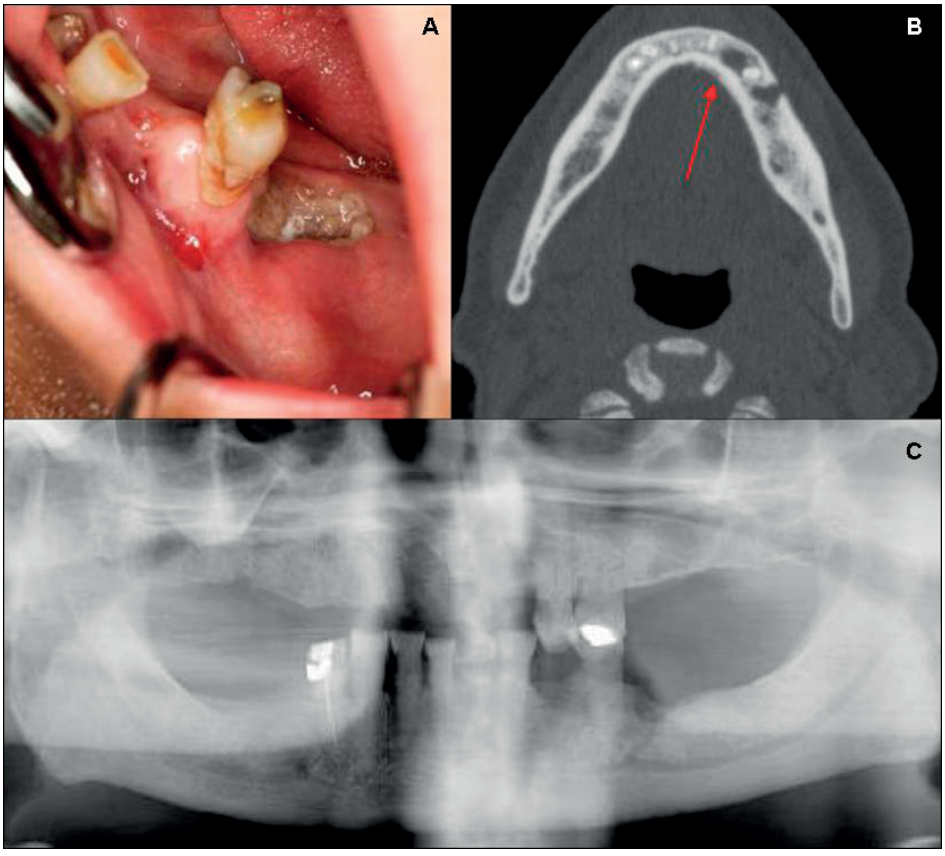
The patient was a 74 year old male, non-smoker who did not drink alcohol. The medical history included diabetes mellitus, hypertension, angina and subsequent coronary bypass in 1996, and prostate cancer in 1994. This was treated with a TURP and chemo-radiotherapy ending in 1995. Lung and skeletal metastasis were identified in 2007.Due to increasing PSA-values in 2000 the patient was treated with bicalutamide and gosereline; dutasteride and calcichew were also given. Bisphosphonates did not feature in his treatment.

In October 2007 he was enrolled into a phase III randomized double blind multicentre trial, testing the efficacy of denosumab with zoledronic acid in the treatment of bone metastases of hormone resistant prostate cancer.

In May 2008 a dehiscence of the oral mucosa developed in the lower left quadrant without sequestration of the underlying bone. In February 2009 he was admitted with swelling of the floor of mouth and tongue of infectious origin, this was treated with surgical drainage and antimicrobials amoxicillin and clavulanic acid (Augmentin). Because of ongoing symptoms he was referred to the Leiden University Medical Center in May 2009.

At presentation intra and extra-oral swelling and an area of brown-colored exposed bone was present in region 34 to 36 (figure 1A), The submandibular swelling later developed into an abscess with fistula. A panoramic radiograph and CT-scan showed sclerosis and lysis in the left mandible (region 33-35) and subperiosteal bone formation (figure 1B+C). Cultures showed

Figure 1 Intra-oral and radiological situation at first presentation in LUMC May 2009



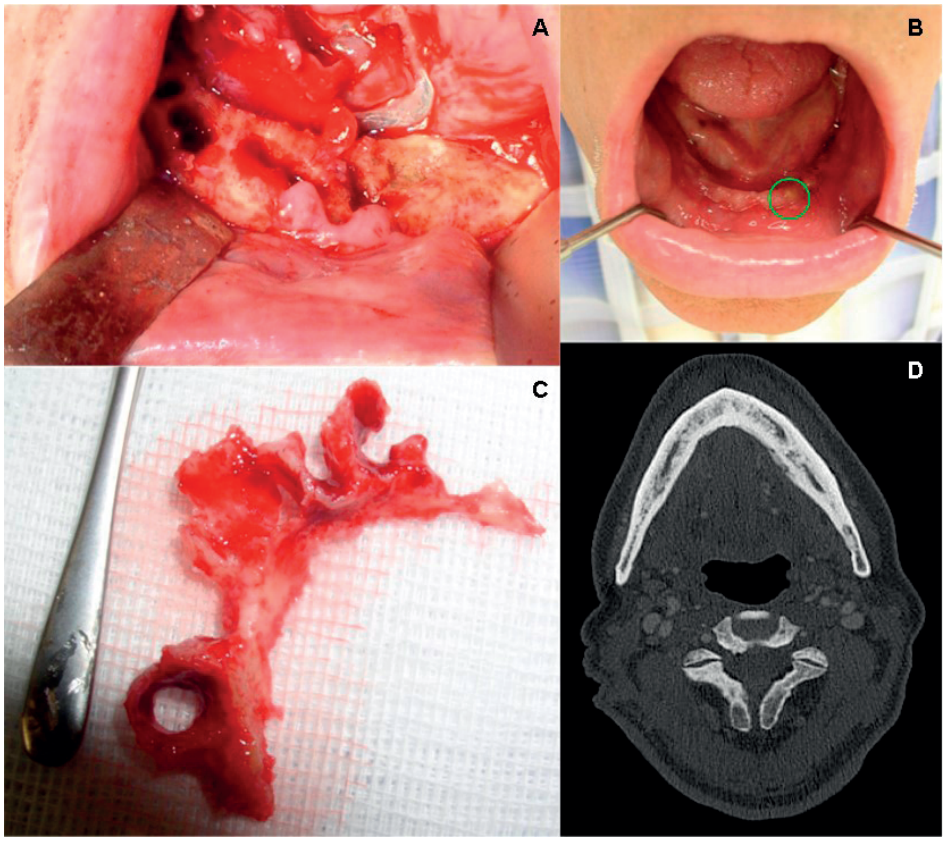
A. Intra-oral view: exposed bone.
B. CT scan: lysis regions 33/35, red arrow: subperiosteal bone formation.
C. Panoramic radiograph: lysis region 33/35.

mixed flora although Actinomyces was not found. The patient was treated by drainage of the abscess and antibiotics for four weeks.

Because of persisting symptoms a sequestrectomy was performed under general anaesthesia with removal of the remaining dentition from the clinically sclerotic bone. The lingual cortex and alveolar process particularly in region 34 to 36 appeared non-vital; bone was lowered and removed (figure 2A+C) until bleeding, relatively viable bone remained. The wounds were primarily closed in a multi-layer technique[5].

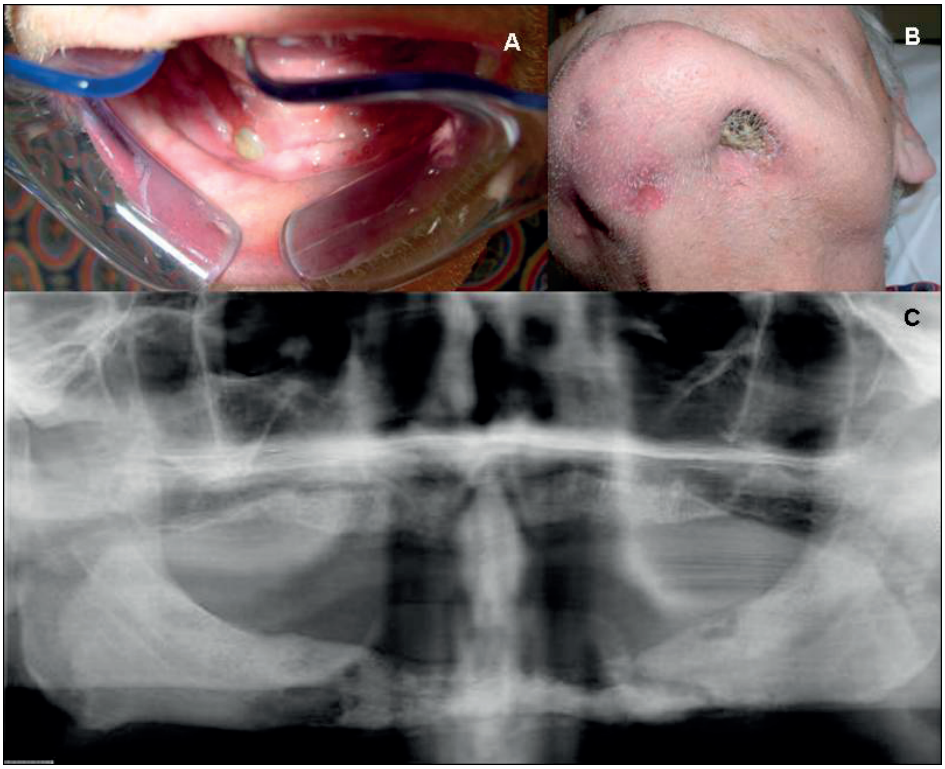
One fistula produced yellow grains, and new cultures at the time of surgery grew Actinomycosis. Penicillin and metronidazole were administered for five days intravenously followed by an eight week oral regime. Histologic examination of the bone showed necrotic bone and areas of extensive remodelling. A mixed-cell infiltrate and Actinomycosis were seen; there were no signs of metastases of the prostate cancer.

Figure 2 First surgery: intra-operative view of third quadrant



A. Intra-oral view in surgery. B. Intra-oral view 3 weeks after surgery with exposed bone, remaining fistula (circle). C. Removed non-vital bone from the alveolar process of the mandible at surgery. D. CT scan 6 weeks after surgery: subperiosteal bone formation at the lingual lower aspect of the left lower jaw.

Figure 3 Six weeks after second surgery



A. Intra-oral view with multiple fistulas and exposed bone. B. Extra-oral view with submental/submandibular fistula, with exposed bone. C. Panoramic radiograph with osteolysis, subperiosteal bone and pathologic fracture in the left lower mandible.

The research group organizing the phase III trial was asked to code break and reveal the drug given to the patient; it was Denosumab. Twice a year he received a subcutaneous injection with a dose of 60 mg Denosumab.

Three weeks after surgery there were again two small areas of exposed bone in the 35 and 44 region (figure 2B), with a discharging extra-oral fistula. Pain had however slowly diminished.

Six weeks after surgery a CT scan showed no large abnormalities besides subperiosteal bone formation (figure 2D).

Sixteen weeks after the first surgery the extra-oral fistula had not disappeared and bone could be probed through it; with new abscess formation a second surgery was performed. During exploration from area 36 to 46 a significant amount of subperiosteal bone formation was seen on both buccal and lingual surfaces. The entire region showed barely bleeding bone and greyish marrow. As much affected bone as possible was removed, up to the point of risking loss of continuity. Again, the wounds were primarily closed in layers. Histologic findings were similar to the first surgery. Cultures showed Streptococcus constellatus, Fusobacterium and Actinomyces, all sensitive to Penicillin, which was given intravenously for five days combined with metronidazole. Amoxicillin was prescribed orally for a further three months.

On the first postoperative day the patient developed neurologic symptoms, found to be as the result of cerebral metastasis of the original prostate cancer (confirmed histologically). He underwent craniotomy to decompress the lesion, the patient recovered and was discharged for rehabilitation.

He was followed up in the out-patient clinic. Complaints of pain had diminished, but the extra-oral fistula and intra-oral dehiscence remained and were slowly progressive (figure 3A+B). The panoramic radiographs showed a slowly deteriorating mandible as shown in figures 3C. Eleven months after the first surgery the patient died of brain metastases from prostate cancer.

DISCUSSION

Bisphosphonates are currently the first drugs of choice when treating bone metastases from e.g. prostate or breast cancer, multiple myeloma and osteoporosis[10]. Prostate cancer is the most common newly diagnosed cancer in men worldwide. Approximately 30 % of postmenopausal women in the US and Europe have osteoporosis[19], and yearly nearly 2 million hip fractures occur in the US as a result of this[20]. These numbers illustrate the large cohort of patients that are potentially eligible for these drugs. A recently highlighted, and well-reported side-effect of this treatment is bisphosphonate osteonecrosis[5].

A new drug in this field is Denosumab, a fully human monoclonal antibody to receptor activator of NF-κB ligand (RANKL), a cytokine member of the TNF family, and the principal mediator of osteoclastic bone resorption[10]. By binding to RANKL, Denosumab prevents the activation of RANK. This results in the inhibition of the maturation of osteoclasts and hence a decrease in their function and subsequent inhibition of osteoclast-mediated bone resorption. In trials it is delivered to the patient by subcutaneous injection several times a year with a dose varying from 60-120 mg[8,9,12-14,16].

Phase I, II and III trials in both patient categories have been published demonstrating that Denosumab has resulted in decreased levels of bone turnover markers[9,15] and significant increases in bone mineral density compared with placebo[9,21]. This has led to a decrease in occurrence of non-vertebral and hip fractures[8,9,15]. Further studies have shown that osteoporotic patients that have used alendronate and have switched to Denosumab have a significantly greater increase in Bone Mineral Density (BMD)[11].

A potential hazard of Denosumab might be that several non-skeletal cells, including activated T and B cells, also express RANK and RANKL; therefore Denosumab could have a negative effect on the immune system. Several Denosumab trials have monitored the side effects[8,9,12,14,16]. A higher incidence of serious adverse effects were found in the Denosumab group compared to the placebo group (34,6 % vs. 30,6 %)[9], this was not significant, although the former group did have a higher rate of infections requiring hospitalization and a higher occurrence of several skin-related conditions. Fizazi et al. showed serious adverse events of 63% vs. 60% of respec-

tively Denosumab vs. zoledronic acid, this was not significant either[12]. They also showed 2% (n=943) of osteonecrosis in the Denosumab group compared to 1% (n=945) in the zoledronic acid group, but with no significant difference. Smith et al. reported 5% (n=720) development of osteonecrosis of the jaws in patients who used Denosumab compared to zero osteonecrosis in patients receiving a placebo[14]. Saad et al. found a low incidence of osteonecrosis of the jaw with Denosumab of 0,9% (n=5723 patients)[16]. One study reported an increased incidence of cataract in the Denosumab group[9].

In this case, there was evidence of infectious symptoms only seven months after start of Denosumab followed by invasion of the mandible and established osteomyelitis not withstanding repeated antibiotic and surgical treatment. Our expectation was that the mandible would ultimately loose its continuity by sequestration.

Although there is an increasing body of literature about bisphosphonate related osteonecrosis, the exact mechanism by which it is caused and develops is still unclear and debated[22].

In this case report about the detrimental effects of Denosumab on the jaw bone a definite model of the working mechanism cannot be given either. However, the patient has not used any other medication aimed at influencing the bone metabolism by suppressing bone resorption. It is for this reason in our opinion there is a clear link between the drug and the disease. We feel reporting this serious, previously unknown side-effect has clinical relevance in the on-going debate on Denosumab.

CONCLUSION

The use of Denosumab may lead to a type of osteonecrosis resembling bisphosphonate related osteonecrosis of the jaws. This is a report of the upcoming serious side-effect of Denosumab.

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