Avascular Mandibular Osteonecrosis in Association with Bisphosphonate Therapy: A Report on Four Patients

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Abstract. Over the past three years, several reports have been published on jaw osteonecrosis possibly being associated with the administration of bisphosphonates. Bisphosphonates are highly active inhibitors of osteoclasts. These drugs are used for the treatment of multiple myeloma, bone resorption in the case of metastatic malignant diseases, tumor-associated hypercalcaemia, and in the treatment of osteoporosis. Due to the importance of this presumed side-effect of bisphosphonates for the dentist and the maxillofacial surgeon, we report four cases. Case Reports: Four patients (two women and two men aged 56, 62, 67 and 75 years, respectively) were diagnosed with osteonecrosis of the mandible. These osteonecroses did not react adequately to local treatment and systemic therapy with antibiotics. One patient suffered from non-Hodgkin’s lymphoma, one from breast cancer, one from prostate cancer and one from sarcoidosis. Besides cytostatic chemotherapies, all patients received bisphosphonates over an extended period. Discussion: Bisphosphonates are considered an established standard in the treatment of multiple myeloma and bone metastases. Over the past few years, a rapidly increasing number of reports have been published describing patients with a history of bisphosphonate therapy in whom therapy-resistant osteonecrosis of jaw bones occurred either after dental extractions or spontaneously. Since then, bisphosphonate therapy has come under scrutiny as a cause of osteonecrosis. However, the multiplicity of drugs prescribed for the treatment of cancer requires caution when determining a cause-and-action effect. Since patients with malignant diseases receive cytostatic therapy and a range of other drugs, including bisphosphonates, enhancement of the side-effects may be presumed. The case report of an osteonecrosis of the jaw following multi-drug therapy for sarcoidosis adds a further and non-cancerous condition to the newly described entity of bisphosphate-associated jaw necrosis. Conclusion: The probable association of the therapeutic use of bisphosphonates and the development of jaw necrosis has to be studied in further investigations. Patients who will undergo bisphosphonate therapy should receive a careful dental check-up prior to drug application. Patients receiving bisphosphonates should be followed up carefully to avoid the occurrence of extended osteonecrotic lesions. Moreover, established jaw lesions must be diagnosed precisely in order to exclude metastatic disease.

The necrosis of the jaws is a severe complication associated with different conditions. Osteonecrosis can occur in patients exposed to X-rays in the treatment of head and neck cancer, in particular following a tooth extraction (1) but can also occur in trauma (2), fungal or bacterial infections (3), or sarcoidosis (4). The association between chemotherapy and jaw osteonecrosis is recognized (5, 6).

Over the past few years several reports have been published on jaw osteonecrosis possibly being associated with the administration of bisphosphonates (7, 8). Bisphosphonates are highly active inhibitors of osteoclasts and are preferentially applied in the treatment of cancer metastatic to bones, multiple myeloma and osteoporosis (9, 10). Metastases to the oral cavity and jaws are rare in the course of cancer (11), indicating a final state of the disease. Osteonecrosis of jaws not associated with distant spread of cancer is also rare. However, the evaluation of osteonecroses in maxillofacial surgery patients did reveal a subgroup of cancer patients whom were treated with bisphosphonates (8, 12).

Due to the importance of the presumed side-effect of bisphosphonates concerning the jaws, in particular in the treatment of cancer patients, we report four cases.

Case Reports

Case 1. The incidental finding of an increased blood sedimentation rate of a 47-year-old male patient was followed by a detailed blood investigation, revealing a monoclonal gammopathy. A bone marrow biopsy confirmed a low-grade Non-Hodgkin’s lymphoma (immunocytoma grade IV). Lymph node or other organ involvement was excluded and the patient received no therapy for the next 13 years. Following a fracture of the thoracic spine at the age of 55 years – obviously not related to the immunological disease – the patient complained...
A 68-year-old female patient was referred to our Case 2. After cessation of bisphosphonate therapy. (Figure 1). The pain of the thoracic spine developed again depicting the severe demineralisation of the affected mandible. Clindamycin and local rinsing with chlorhexamed. Radiographs of the left cheek that was successfully treated with cycles of antibiotics (amoxicillin and clavulan acid) were administered for 2 months. However, the patient again developed pain in this region compared to the skeletal system indicative of osteomyelitis. Intraorally, the alveolar ridge of the right molar region perpetuated by a bone surface. Again, wound healing was not achieved and a further local revision was performed 3 months later, including decortication, necrosectomy of bone and a neurolysis. Antibiotics (amoxicillin and clavulan acid) were administered for 2 months. However, the patient again developed pain in the left mandible. A further decortication was performed four months after the previous intervention. A biopsy of the right side of the mandible revealed no local infection or necrosis and healing proved uneventful. Clindamycin was administered alternatively.

At the age of 62 years, two years after starting with bisphosphonates, the patient developed pain in the left mandibular molar region. Tooth 36 (first molar) was extracted. The wound did not heal and pain did not diminish. Six months later the fistula at the extraction site was excised, accompanied with a decortication of the mandible, neurelisis of the mental and alveolar branch of the trigeminal nerve and the osteotomy of tooth 35 (second mandibular premolar). Histology revealed an osteomyelitis and spores of actinomycetes covering the dead bone surface. Again, wound healing was not achieved and a further local revision was performed 3 months later, including decortication, necrosectomy of bone and a neurolysis. Antibiotics (amoxicillin and clavulan acid) were administered for 2 months. However, the patient again developed pain in the left mandible. A further decortication was performed four months after the previous intervention. A biopsy of the right side of the mandible revealed no local infection or necrosis and healing proved uneventful. Clindamycin was administered alternatively.

At the age of 64 years the patient was admitted to our outpatient clinic due to a recurrent painful swelling of the left cheek. Intraorally the mandible was exposed in the left premolar region. At the time of admission we had no data on the history of immunocytoma or the current bisphosphonate therapy, possibly not communicated by the patient due to a chronic brain disorder following chronic alcohol abuse. After an initial antibiotic therapy with oral administration of clindamycin, we again performed a decortication. In this instance pain-relief was achieved, however, soft tissue closure was only short-term. Histological investigation revealed a plasmacellular osteomyelitis with sclerosing bone, including osteones and fibrosis of bone marrow spaces, resembling an osteoma. Further contact with the patient enabled us to complete the medical history of this claustrophobic patient. Bisphosphonate therapy was stopped. Within the last 12 months the patient twice developed a painful swelling of the left cheek that was successfully treated with cycles of clindamycin and local rinsing with chlorhexamed. Radiographs depict the severe demineralisation of the affected mandible (Figure 1). The pain of the thoracic spine developed again after cessation of bisphosphonate therapy.

Case 2. A 68-year-old female patient was referred to our outpatient clinic for the treatment of an ulcer of the right mandibular alveolar ridge that had developed over the previous few weeks. The patient had been suffering from breast cancer since the age of 65, becoming symptomatic with a spontaneous rib fracture, but diagnosis was delayed for 7 months after bone affection (T4N2M1). Therapy started with letrozole (aromatase inhibitor), external irradiation for vertebral column metastasis and zoledronic acid (Zometa). Therapy proved to be effective in terms of tumor reduction. Ablative surgery of the affected breast and efferent lymphatics was carried out at the age of 66.5 years and was combined with irradiation of the ipsilateral thorax. About 10 months later, multiple bone metastases were diagnosed. Letrozole was replaced by Aromasin™ (exemestane). About 2 months later creatinine levels increased to 1.8 mg/dl that led to cessation of zoledronic acid (applied over 18 months). One month later a bone marrow carcinosis and thrombocytopenia were diagnosed (bone marrow biopsy: 100% tumor cell invasion; whole body scintigraphy: disseminated bone marrow invasion). Pharmacological treatment was restricted to mitoxantrone, followed after a few weeks by the application of Aredia™. Two months later the patient developed a non-healing ulcer of the mandibular alveolar ridge of the right molar region perpetuated by a partial denture covering the toothless molar regions. Scintigraphy had depicted a relative increase of the activity in this region compared to the skeletal system indicative of osteomyelitis. Intraorally, the alveolar ridge of the right side of the mandible was exposed to a diameter of about 10 mm. This defect caused recurrent pain. Treatment was restricted to local wound cleaning, oral antibiotics and covering the exposed bone with aureomycin-gauze. The local findings remained stable over 6 months while the tumor progress was not substantially stopped under cytostatic and bisphosphonate treatment.

Case 3. A female patient developed diabetes mellitus at the age of 59 years. The patient became insulin-dependent at the age of 72 years. A hypertonus and coronary artery disease were diagnosed at the age of 70 years. About one year after the commencing insulin substitution hypercalcemia was found. A bone marrow biopsy revealed a granulomatous epitheloid cell reaction suspected of being indicative of sarcoidosis. A corticosteroid medication was started leading to a reduction of bone invasion. However, the medication was accompanied by a substantial increase in body weight. Reduction of corticosteroids was followed by immediate hypercalcemia and increase of angiotensin converting enzyme (ACE) 180 U/l. Therefore, the corticosteroid medication was reinforced (10 mg prednisolone/d). A bisphosphonate therapy had been started at the age of 72 years (zoledronate) and was administered intravenously up to the age of 75 years.

At the age of 75 years the mandibular left wisdom tooth was extracted. The wound did not heal. A revision of the...
extraction site and decortication of bone was performed 3 months later, revealing osteonecrosis. However, wound healing was incomplete and pain relief was only temporary. A continuity-saving partial mandibular resection was performed 6 months later. Six months after this intervention a residual mucosal lesion persisted but the patient has no pain and no signs of local inflammation.

**Case 4.** The medical history of a 56 year-old-male patient revealed a hormone-refractory metastasizing carcinoma of the prostate. Eleven years prior to the referral, the prostate carcinoma (pT3a, N0; Gleason 3+4=7) was diagnosed which led to radical prostatectomy. Seven years later local recurrence occurred after which the prostate lodge was irradiated. Six months later the prostate-specific antigen (PSA) levels further increased prompting a therapy with an LHRH-agonist (luteinizing hormone-releasing hormone). Ten months later, during a bicycle excursion, the patient registered a sudden pain in the lower spine. The imaging revealed an osteolytic lesion characteristic of an ossary metastasis of the 3rd lumbar vertebrae terminating in fracture of the spinal segment. An oral bisphosphonate was prescribed (Ostac™, clodron acid). A therapy with Flumid™ (flutamide) was allotted, which was substituted four months later.
later due to a continual PSA level increase by Estracyt™ (estramustinephosphate). The lower spine was irradiated with 40 Gy after which an intravenously administered bisphosphonate (zoledronate, 8 mg once a month) was added. Seven months later, chemotherapy with two cycles of anthracycline MEN 10755 was administered without noteworthy success, so that a further six cycles of Taxotere™ (docetaxel) were given. Proving therapy-refractory, a further chemotherapy with Navelbine™ (vinorelbine) was allotted without achieving reduction in tumor progress. Finally an oral chemotherapy with Ixoten™ (trofosfamide) was allocated.

At the time of referral the patient had completed the chemotherapy with Taxotere™. The treating dentist extracted the lower right wisdom tooth alio loco but the alveolus showed no signs of healing. The patient complained of pain. An oral antibiotic with clindamycin (3x300 mg/d) was implemented. The alveolus was packed with gauze and irrigated every two days as a local therapy. The symptoms refused to subside under this therapy with the defect showing no signs of healing. The patient was admitted to hospital for local revision of the defect under general anaesthesia. A marginal resection of the lower mandible was performed and the adjacent tissue was histologically analysed to exclude metastasis of the prostate carcinoma. The examination revealed necrosis of the adjacent osseous tissue without features specific for metastasis. The postoperative healing proved uneventful with complete epithelialization of the resection site. Six months later the patient had to be readmitted to hospital having suffered a fracture of the mandible in the region of the previously performed resection.

A reconstruction plate (Synthes 2.4) was introduced transorally and a mandibular-maxillary fixation was allotted without achieving reduction in tumor progress. Finally an oral chemotherapy with Ixoten™ (trofosfamide) was allocated.

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A reconstruction plate (Synthes 2.4) was introduced transorally and a mandibular-maxillary fixation was allotted for 3 weeks. Postoperative healing proved uneventful. The patient died 5 months later from the primary disease.

Discussion

These reports demonstrate the association of mandibular osteonecrosis with bisphosphonate-treatment in different entities: metastatic breast and prostate cancer, hypercalcemia in the course of sarcoidosis, and a low-grade non-Hodgkin’s lymphoma with bone pain following a spinal fracture. Two patients suffered from internal diseases over a long period of time and all had further cytotoxic medications at the time of osteonecrosis. Three of the patients developed osteonecrosis in the course of tooth extraction, whereas one patient developed the lesion due to pressure from a cover denture. These reports substantiate the association of bisphosphonate exposure and jaw osteonecrosis, but not the causation by these drugs.

Bisphosphonates are used for the treatment of multiple myeloma (10), bone metastasis of malignant disease (9), tumor-associated hypercalcaemia, the treatment of osteoporosis (13) and osteogenesis imperfecta (14). It is estimated that the frequency of jaw osteonecrosis after bisphosphonate therapy is 1 patient in 10,000 (15, 16). It is yet unknown why the avascular necrosis preferentially affects the jaws. Possible risk-factors of osteonecrosis in this condition are the diagnosis of cancer (with chemotherapy or radiotherapy), co-morbid conditions, including poor oral hygiene and osteomyelitis, anemia and disorders of blood coagulation (15, 17). The majority of bisphosphonate-associated reports point to the fact that intravenous administration has a higher risk than oral therapy (8). Oral bisphosphonates are currently under intensely investigation in the treatment of metastasizing breast cancer (9).

Bisphosphonates are not metabolized and have a strong binding to osteoclasts thus remaining in bone for months or years. Therefore, the cessation of bisphosphonate therapy does not appear to support the recovery of bone from osteonecrosis.

Surgical treatment or radiotherapy was cited as triggering the osteonecrosis in the majority of cases (8). However, recent reports showed that osteonecrosis can occur in patients with no previous treatment of the jaws (18).

The application of bisphosphonates outside the main fields of application (osteoporosis, bone metastases), however, is recommended for certain maxillofacial conditions, e.g. the treatment of monostotic fibrous dysplasia (19). Even the cessation of jaw osteomyelitis was documented following bisphosphonate administration [alendronate (20)]. This had already been reported for the treatment of hip osteomyelitis (21).

In the experimental setting, bisphosphonates combined with tetracycline reduced alveolar bone loss in rats (22) and bisphosphonate was effective in promoting bone healing of cementless metal implants (23). Clinical application of bisphosphonates had no obvious adverse effect on the integration of dental implants in a patient (24), the alveolar bone resorption following tooth extraction (25), or in the treatment of periodontitis (26, 27), in particular in post-menopausal women (28). However, osteonecrosis was reported in periodontal patients who were treated with bisphosphonates (29) and dental implants were lost in a patient who started bisphosphonate therapy (30).

The number of reports dealing with an association of bisphosphonate-therapy and jaw necrosis is increasing rapidly. However, it was calculated that about 2.5 million patients worldwide have used bisphosphonates (pamidronate and zoledronate) and only in rare cases does a jaw osteonecrosis occur (16). Finally, it should be kept in mind that the chemotherapy for cancer might be associated with jaw osteonecrosis (5) and that the reported bisphosphonate-treated diseases might themselves be associated with (jaw) osteonecrosis, without bisphosphonate treatment (4, 31).
Conclusion

Patients who are to receive bisphosphonate therapy should be warned about the potential side-effects concerning the jaws (15, 32). A thorough oral examination is recommended prior to bisphosphonate therapy. It time permits before initiation of the drug application, treatment of tooth or jaw problems that could predispose to osteonecrosis should be completed.

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