VIA MEDICA

CASE REPORT

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Biphosphonates-related osteonecrosis of the jaw

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ABSTRACT

The relationship between osteonecrosis of the jaw and bisphosphonate therapy has been described recently. Although bisphosphonates have a long list of benefits in the treatment of patients with bone metastases, an increasing number of reports describe the complication of bisphosphonate-related osteonecrosis of the jaw (BRONJ). Bisphosphonates are synthetic analogues of pyrophosphate that inhibit bone resorption. The aetiology of BRONJ is unclear. It starts as aseptic necrosis, with a surgical procedure involving an interruption in the continuity of the oral mucosa as an obligatory precondition. Subsequently, areas of osteonecrosis occur and detach from the surrounding areas of purulent inflammation or can be removed surgically. Due to the limited treatment options, conservative treatment supported by antibiotic and surgical therapy is used. This article describes a case of BRONJ.

Key words: bisphosphonate, osteonecrosis, jaws, osteoporosis

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Introduction

Bisphosphonates are medicines useful in patients with bone metastases originating in primary breast, prostate and kidney cancers, multiple myeloma and Paget's disease [1]. Bisphosphonates are also used by patients with osteoporosis [2, 3].

The multi-directional activity of these drugs with their inhibitory effect on bone resorption has many benefits but is also burdened by adverse effects [4]. A particular adverse effect affecting the oral cavity is bisphosphonate-related osteonecrosis of the jaw (BRONJ).

It is defined as an area of exposed bone in the maxillofacial region which does not heal within 8 weeks in a patient currently or previously treated with bisphosphonates and not subjected to radiation therapy of the head or neck [5, 6, 7].

The disease is mainly associated with intravenous administration of high doses of bisphosphonates, but cases of BRONJ in patients treated with low oral doses have also been observed [8]. Treatment and prosthetic rehabilitation of the affected patients are difficult and very limited.

Case description

A patient receiving treatment for breast cancer. In 1997, right-side mastectomy was conducted due to cancer, followed by chemotherapy and radiation therapy. In 2002, a local recurrence was detected along with metastases to the spine and the supra- and infraclavicular lymph nodes on the right side. In 2005, metastases to the shoulder tissues were detected. Type 2 diabetes mellitus. The patient was treated with bisphosphonates between July 2002 and May 2017. Treatments used include, inter alia, clodronic acid, 90 mg every 4 weeks, i.v. (Jul 2002–Oct 2005), pamidronic acid, 60 mg every 4 weeks, i.v. (Nov 2005–Feb 2011), zoledronic acid, 4 mg every 4 weeks, i.v. (Mar 2011–May 2017). In 2011, the patient underwent maxillary tooth extractions. The alveoli were not closed with stitches. Not all post-extraction wounds healed, and osteonecrosis occurred in the incisor area. The patient was hospitalized several times due to pain in the area. In January 2018, maxillofacial CT with contrast revealed "loss of the right-side alveolar process of approx. 30×16×17 mm without separation of pathological mass — necrosis?" (Fig. 1).

In April 2018, the patient reported pain in the area and leakage of fluid through the nose during drinking. In physical examination, exposed right-side maxillary alveolar process between the alveoli for teeth 11 to 13, reaching the vestibular fornix (Fig. 2). Increased oral hygiene recommended.

Discussion

In terms of chemical structure, bisphosphonates are synthetic analogues of pyrophosphate (natural

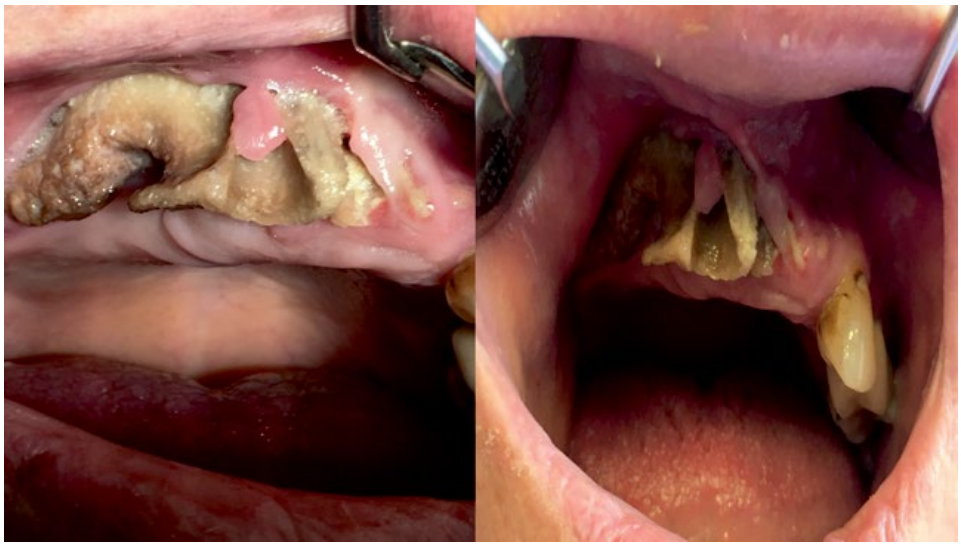

Figure 1. Current CT image — red arrows indicate a bone loss in the maxilla

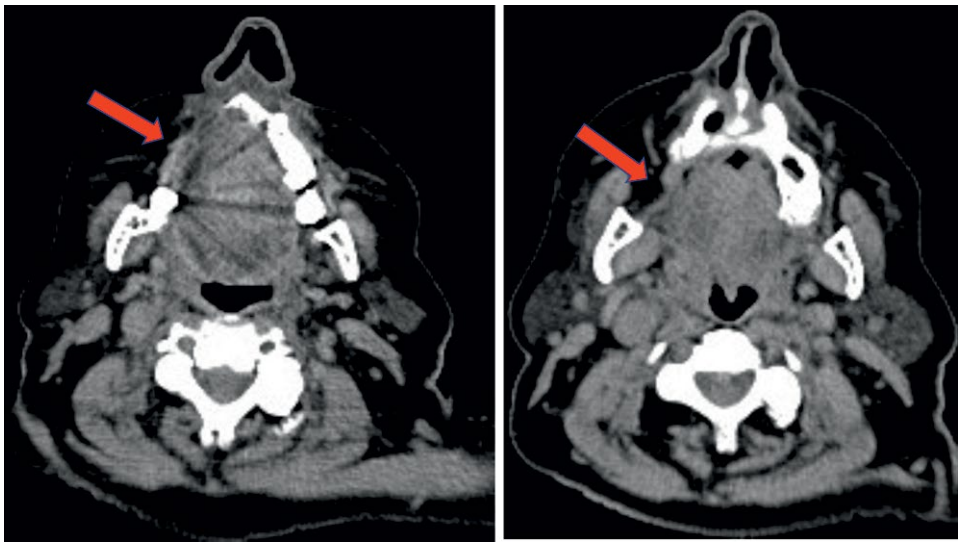

Figure 2. The current image of alveoli

regulator of bone mineralization) in which the central oxygen atom has been replaced by a carbon atom. Two additional side chains R1 and R2 are bound to the carbon atom. R1 is usually a hydroxyl group. Depending on the composition of R2, bisphosphonates can be divided into two major groups:

1. Simple (non-nitrogenous) bisphosphonates — without nitrogen in the R2 composition.
2. Nitrogenous bisphosphonates (aminobisphosphonates) — containing nitrogen in the R2 composition, including alendronate, zoledronate, pamidronate, risedronate, ibandronate [9, 10].

Bisphosphonates have a high affinity to hydroxyapatite crystals in bone, which they bind via two phosphate groups and the R1 side chain that together form the "bone hook" 11].

Aminobisphosphonates with a long side chain containing nitrogen cause disruption of the osteoclast intracellular signalling system, which results in the inhibition of the metabolic activity of mature osteoclasts. The clinical effect of aminobisphosphonates is inhibition of bone resorption [9].

Approximately 60% of the administered dose is deposited in areas of active bone mineralization, and its half-life is approximately 10 years. The non-deposited fraction is excreted by the kidneys [8]. The aetiology of BRONJ is unclear. It is caused by the exposure of maxillary or mandibular bone due to an interruption in

the continuity of the mucosa, e.g., during dental procedures or as a sequela of denture-related sores [10].

Because of the constantly applied pressures associated with chewing, the mandible and the maxilla are characterized by a greater bone turnover than other skeletal regions (e.g., 10–20 times greater than in the ilium) [12]. This intensity of bone turnover is necessary to repair microfractures arising during chewing. Concurrently, it requires a higher degree of vascularization, which is crucial in bisphosphonate therapy, allowing a higher concentration of these drugs in the bone tissue in that area [13]. The oral mucosa is thin and susceptible to damage, which facilitates bacterial infection of the exposed bone [14, 15].

Maxillary BRONJ leads to the formation of osteonecrotic areas. The disease presents similarity to radiation therapy-induced osteonecrosis, starting as aseptic necrosis of bone. Aseptic necrosis is usually caused by insufficient blood supply [16, 17].

In recent years, it was noted that similar lesions can occur in patients after treatment with denosumab (anti-RANKL IgG2) and bevacizumab (anti-VEGF antibody reducing tumour vasculature) [18], regardless of previous bisphosphonate therapy. There is also a number of factors that increase the risk of BRONJ. Among them, in the course of multiple myeloma, a likely genetic factor can be distinguished — polymorphism of the CYP2C8 gene that is linked to the arachidonic acid cycle and is a regulator of vascularization, which in the mandible could lead to poorer vascularity and increased risk of BRONJ (up to 12.5 times) [19].

Other BRONJ risk factors include glucocorticosteroids (chronic therapy adversely affects bone metabolism, weakening osteoblast differentiation and function). Furthermore, the immunosuppressive and antiangiogenic effect of glucocorticoids can play a major role in the development of necrosis [20–22].

The frequency of BRONJ increases from 1.5% (in patients treated for 4–12 months) to 7.7% (in patients treated for 37–48 months) [23].

The risk of this disease can also be increased by [24]: High alcohol consumption, smoking, anemia, chemotherapy, diabetes mellitus, obesity, renal failure, rheumatoid arthritis, immunosuppression, older age (risk increases by 9% per decade of life), female gender (maxillary BRONJ is 8 times more frequent in women than in men).

Local factors include [20] anatomical structures involving compact bone covered by a thin layer of mucosa, such as bony prominences or tubercles, periodontal diseases, including spontaneous tooth loss, surgical interventions related to the interruption in the continuity of oral mucosa, such as tooth extractions, periodontal treatments (scaling, curettage), placement of dental implants, endodontic therapy (when the tool is moved beyond the tip of the tooth root), misfitted dentures, poor oral hygiene.

The disease is usually diagnosed clinically. As a result of the lack of healing, areas of osteonecrosis occur and detach from the surrounding areas of purulent inflammation. The process is accompanied by pain, numbness, soft tissue oedema, hyperesthesia, tooth loosening, suppuration, and intra- and extraoral fistulas. Although these symptoms can develop spontaneously, BRONJ is much more frequent after surgical interventions on alveolar processes involving an interruption in the continuity of the mucosa and periodontium [8].

In some cases, necrosis develops asymptomatically and is clinically undetectable, with the patient being unaware of the disease for weeks or months. The first symptoms preceding clinically developed necrosis can include pain, mucosal ulceration, erythema and oedema, and tooth loosening [20]. In maxillary BRONJ, abscesses can reach the supra canine and buccal spaces [25]. In mandibular BRONJ, abscesses can be located in the submental, submandibular and sublingual spaces [26]. The difference in compactness between the maxilla and the mandible causes a different course of inflammation in these bones. In the maxilla, suppuration is manifested by a fistula, while in the mandible, suppuration spreads within the bone and rarely reaches its surface [27].

Three stages of progression of BRONJ have been distinguished [28].

Stage I — exposure of bone without oedema and erythema of the surrounding soft tissue, without radiological changes; pain can occur before bone exposure.

Stage II — primary or secondary inflammation of the soft tissue surrounding the exposed bone, pain, tooth loosening. Necrotic lesions in the radiological image can resemble periapical radiolucency, broadening of the periodontium or thickening of the alveolar lamina dura.

Stage II — primary or secondary inflammation of the soft tissue which is difficult to treat with oral or intravenous antibiotic therapy; the presence of extraoral fistulas. If the lesion affects the mandible, hypoesthesia of the lower lip can occur, and when the maxilla is affected, secondary maxillary sinusitis can develop. In the radiological image, a visible increase in radiolucency, pathological fractures of the mandible, necrotic areas, as well as osteitis-like and metastasis-like lesions can be found.

As has been reported in the literature, bacteriological tests can reveal the presence of *Staphylococcus epidermidis*, *Streptococcus salivarius*, *Morganella morganii*, *Prevotella intermedia* and *Prevotella oris*, as well as *Escherichia coli* — Gram-negative rods. In half of the cases, the exposed bone is colonized by *Actinomyces* strains [29].

Table 1. Methods of treatment of BRONJ [4]:

Stage of progression	Definition	Treatment
Stage I	— Loss of oral mucosa with bone exposure which can be preceded by pain — No radiological signs — No features of infection, edema or soft tissue erythema	Conservative (flushing of the oral cavity with, e.g., 0.12% chlorhexidine solution)
Stage II	— Loss of oral mucosa with bone exposure — Clinical features of infection — Soreness, tooth loosening — In X-ray, increased radiolucency, thickening of the alveolar lamina dura	Conservative (flushing of the oral cavity with, e.g., 0.12% chlorhexidine solution, and antibiotic/antifungal therapy)
Stage III	— Loss of oral mucosa with bone exposure — Clinical features of infection with pain — Signs, such as: fistula, pathological fracture, osteolysis, impaired sensation, sinusitis — In X-ray, increased radiolucency, necrotic areas, osteitis	— Surgical (resection of necrotic tissue or resection with vascularized bone grafting) — Antibiotic/antifungal therapy

The diagnosis of BRONJ is based on anamnesis, physical examination, clinical presentation and diagnostic imaging, usually pantomography or CT.

Treatment of patients with BRONJ is difficult. Treatment methods depending on the stage of progression and the extent of necrosis are shown in Table 1.

Conclusions

BRONJ is an increasingly observed complication following treatment procedures in the oral cavity of patients concurrently or previously receiving bisphosphonates. It is a very painful disease that is difficult to treat. Dental practitioners should be made more aware of the need for detailed anamnesis before conducting procedures that involve an interruption in the continuity of the oral mucosa. Previous treatment of oral problems in patients beginning bisphosphonate therapy, greater awareness of the need to inform the dentist of all medications taken currently and, in the past, as well as periodic checks and stricter hygiene regime might contribute to a reduction in the frequency of this complication.

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