

BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS – REPORT OF THREE CASES IN BULGARIA AND REVIEW OF THE LITERATURE

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SUMMARY – A severe complication of the administration of bisphosphonate-containing medications is known as bisphosphonate-associated osteonecrosis of the jaws (BONJ). A case series of three patients affected by BONJ is presented. These patients currently represent the only described cases of BONJ in Bulgaria. Exposed necrotic bone of the mandible was observed in two patients and the maxilla was affected in the third case. Two of the patients had been treated with zoledronate for metastatic prostate cancer and one patient for metastatic endometrioid cancer. All three patients underwent surgical treatment. One of the patients received conservative surgical debridement, i.e. removal of necrotic bone only, and primary wound closure. Conservative surgical debridement and application of local medications without wound closure were used in the other two patients. All three patients received systemic antibiotic treatment. No evidence of disease progression was observed during the follow-up period of 3 to 12 months. The surgical approach utilized in the present study is discussed in the light of the etiopathogenesis, prevention and treatment of BONJ.

Key words: *Osteonecrosis – surgery; Jaw diseases – chemically induced; Bisphosphonates – adverse effects; Surgical operative procedures*

Introduction

Avascular osteonecrosis of the jaws is a serious complication associated with the use of bisphosphonate medications¹. It is known as bisphosphonate-associated osteonecrosis of the jaws (BONJ) and has been reported widely in the literature in the past 6 years. BONJ has been defined as necrosis, associated with or unrelated to dental procedures, which persists for more than 6 to 8 weeks² and is refractory to conservative treatment³. It should occur in patients who have not received any radiotherapy in the affected area, but

have been treated for a disease characterized by bone resorption with bisphosphonates intravenously for at least one year, or orally for a much longer period. The incidence of BONJ, as reported in the literature, ranges between 1.3%² and 10%⁴. At present, there is disagreement on the treatment of BONJ due to only few evidence-based studies⁵⁻⁹. Therefore, efforts are focused on the opportunities for its prevention¹⁰.

The aim is to report on the first series of three patients with BONJ in Bulgaria, diagnosed and treated surgically at Department of Maxillofacial Surgery, Plovdiv, Bulgaria.

Case Reports

A 73-year-old male patient presented with a chief complaint of pain in the frontal aspect of the upper

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Fig. 1. A patient with bisphosphonate-associated osteonecrosis of the anterior maxilla.

jaw where the frontal teeth had fallen out spontaneously. The patient was diagnosed with metastatic prostate carcinoma 40 months before his presentation. He had received 4 mg of zoledronate (Zometa[®]) in intravenous infusions on a monthly basis during this period. No radiotherapy in the head and neck area had been performed. Intermittent pain had been present



Fig. 2. Computed tomography scan of the maxilla in the patient with bisphosphonate-associated osteonecrosis of the jaws.

in the upper jaw for 21 months after the beginning of bisphosphonate administration. Exposed bone with necrotic appearance, dark brown in color and with porous surface was found on the labial side of the maxillary anterior alveolar ridge. The lesion dimensions were 4 to 6 cm in diameter and it was surrounded by hyperemic gingiva, which was extremely painful to palpation. The second left and right maxillary incisors were mobile and painful, with purulent discharge from the periodontal pockets (Fig. 1). Diagnostic investigations consisted of a panoramic radiograph and computer tomography (CT) without contrast for the exact measurement of the lesion. The radiograph demonstrated bone resorption and CT investigation confirmed the presence of osteonecrotic areas in the anterior maxilla, described as multiple lesions of low density and oval, round and strip-like shapes (Fig. 2). The second left and right maxillary incisors were not salvageable and had to be extracted; the wounds were sutured. Debridement of the necrotic area was carried out under local anesthesia. There was no possibility of primary closure with flap from adjacent tissues. The remaining exposed bone above the sutured extraction wounds was treated with antibiotic ointment (gentamicin cream 0.1%, Actavis, Bulgaria) daily for a week. After the pain and signs of suppuration disappeared, local treatment was changed to the application of 5.0% Solcoseryl (Solco Ltd., Australia) twice *per day*. Systemic antibiotic treatment included intravenous administration of benzylpenicillin sodium (Penicillin G[®], Balkanpharma, Bulgaria) four times daily in doses of 2 000 000 IU for 10 days, followed by phenoxymethyl penicillin (Ospen[®], Sandoz GmbH, Austria) in coated tablets of 1500 IU three times daily for 15 days. The pathology investigation of the necrotic bone confirmed bisphosphonate-associated osteonecrosis of the maxilla with findings of necrotic bone and degenerated stratified squamous epithelium without presence of actinomyces colonies (Fig. 3). During the follow-up, the patient no longer complained of pain. The local signs of inflammation disappeared. The exposed bone was continually treated locally as noted. The patient is still under observation.

A 54-year-old female patient presented with a painful swelling under the right and left lower jaw. The swelling was recurrent and first appeared after the placement of complete dentures six months before her

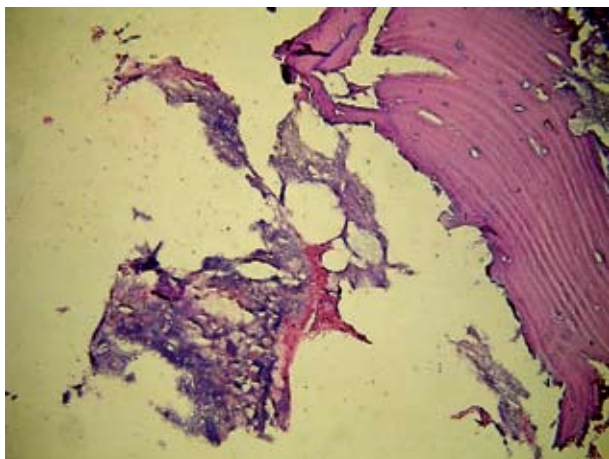


Fig. 3. Microscopic view of necrotic bone in bisphosphonate-associated osteonecrosis of the jaws.

first examination at Department of Maxillofacial Surgery. The patient had been diagnosed with metastatic endometrioid carcinoma 45 months before her referral, and was surgically treated for cancer. She received a total of 42 courses of zoledronate (Zometa[®]) in intravenous infusions of 4 mg monthly. No additional chemotherapy was used. The complete dentures were fabricated 36 months after the start of bisphosphonate treatment. The clinical intraoral examination revealed hyperemia of the oral mucosa of the buccal vestibule of the anterior mandible on the right and exposed bone on the lingual side of the posterior mandible on the left. The bone surfaces in the anterior labial region on the right and the posterior lingual region on the left were exposed by a mucoperiosteal flap under local anesthesia. The bone was presented with porous structure and white chalk color. The macroscopically altered bone was removed by curettage and subsequent grinding, and examined pathologically. The pathology result reported bone tissue with necrosis, but without actinomyces colonies. Wound healing was uneventful. The patient underwent a 14-day course of intravenous administration of benzylpenicillin sodium (Penicillin G[®], Balkanpharma, Bulgaria) four times daily in doses of 2 000 000 IU, followed by a 30-day course of oral phenoxymethyl penicillin (Ospen[®], Sandoz GmbH, Austria) in coated tablets 1500 IU three times daily. No pain was present at the follow-up examination 1 month after the surgery. The patient is being followed up and an assessment of the need for

renewing bisphosphonate treatment is to be made by her oncologist.

A 78-year-old male patient presented with severe pain and swelling in the left half of the lower jaw, which had started several days before the examination. The lower first left molar had been extracted more than three months before, but the extraction wound had not healed yet. The patient was surgically treated for metastatic prostate cancer. The patient had received 18 courses of zoledronate (Zometa[®]), 4 mg in intravenous infusions monthly before presenting to the Department of Maxillofacial Surgery. Medical history also showed diabetes type 2 and anemia. On clinical examination, a non-healed, open extraction wound was visible. The bone had yellowish color and putrid smell. The surrounding mucosa demonstrated signs of inflammation and was markedly painful on palpation. CT examination of the head and neck revealed an irregular, hypodense bone defect in the horizontal ramus of the mandible, which disrupted the continuity of the lateral cortical plate. Surgical debridement with curettage without primary flap closure was performed under local anesthesia. Pathology reported a diffuse and pronounced inflammatory process with a large number of leukocytes and signs of transition to chronic state. No signs of malignancy and no presence of actinomyces colonies were found. The exposed bony surface was treated daily with antibiotic ointment packing (0.1% gentamicin cream, Actavis, Bulgaria). At the follow-up examination 1 month after surgery, the pain had subsided, and pus formation had ceased. Treatment was continued by alternating local application of antibiotic ointment (0.1% gentamicin cream, Actavis, Bulgaria) and 5.0% Solcoseryl (Solco Ltd., Australia). The patient also received cefotaxime (Tchaikapharma, Bulgaria), 3.0 g *per* day intravenously for 7 days. At discharge, the patient had no pain or signs of inflammation. Conservative local treatment of the bisphosphonate-associated necrosis of the jaw continued, with close follow-up of the patient's oral status.

Patient data are summarized in Table 1.

Discussion

Bisphosphonates are synthetic analogues of inorganic pyrophosphates with powerful inhibitory effect on osteoclastic activity. They get incorporated in skeletal bone. Bisphosphonates bind to Ca²⁺ in regions of

Table 1. Summary of cases with bisphosphonate-associated osteonecrosis of the jaws

| | | | |
|--------------------------------------|--|-------------------------------------|--|
| Age and sex | 73/male | 54/female | 78/male |
| Diagnosis | Prostate cancer | Endometrioid cancer | Prostate cancer |
| Oral precipitant | Spontaneous | Pressure spots from total denture | Dental extraction |
| Affected jaw | Maxilla | Mandible | Mandible |
| Type of bisphosphonate | Zoledronate (Zometa ^R) | Zoledronate (Zometa ^R) | Zoledronate (Zometa ^R) |
| Route of administration | IV | IV | IV |
| Duration of bisphosphonate treatment | 40 months | 42 months | 18 months |
| Treatment | Local debridement & conservative treatment | Local debridement & primary closure | Local debridement & conservative treatment |
| Outcome | No progression after 12 months | No progression after 3 months | No information |

high bone turnover, and remain integrated in the bone for more than 10 years¹¹; for example, the half-life of alendronate is assumed to be 12 years. Once incorporated, they start a cascade of biochemical processes resulting in the loss of the ability of osteoclasts to resorb bone, or even in apoptosis. They are used in the treatment of diseases characterized by a high level of bone resorption, such as multiple myeloma, osteolytic bone metastases, Paget's bone disease¹², fibrous dysplasia¹³, McCune-Albright syndrome¹⁴, tumor-induced hypercalcemia, and osteoporosis. More than 2.5 million patients worldwide are assumed to be treated with bisphosphonates¹⁵.

BONJ could be the result of bone metabolism suppression found after bisphosphonate treatment and due to the accumulation of physiologic micro-injuries to jaw bones compromising their biomechanical properties¹⁰. Trauma and infection increase the need for bone remodeling, which exceeds the capacity of the hypodynamic bone and leads to localized bone necrosis. Sook-Bin Woo *et al.*¹⁰ assume that bisphosphonate-associated osteonecrosis develops only in jaw bones because they are insufficiently protected as compared to other bones in the body. It is essential that they are shielded against possible intraoral trauma only by the thin mucosa and periosteum. The presence of teeth in the jaws is a precondition for easy invasion of microorganisms and development of bony infections, by way of dental caries complications and periodontal disease. An interesting fact is that oral bone appears to be particularly resistant

to infection even if the mucosal layer covering the bone is disrupted. Probably human beta-defensin antimicrobial peptides 1, 2 and 3 in jaw bone could be the mediator of innate immunity¹⁶.

All of the reported patients received bisphosphonates for their bone metastases from carcinomas (prostate and endometrioid). Literature data show that bisphosphonate treatment is most frequently used in patients with multiple myeloma because of bone involvement and lung cancer with metastasis in the bones^{4,10}.

All patients in the present study were treated with intravenous administration of amino-bisphosphonate, zoledronate (Zometa^R). According to Dannemann *et al.*¹⁷, all cases of osteonecrosis of the jaws described prior to 2006 were associated with the administration of bisphosphonates containing an amino group. Published reports disagree on the question which amino-bisphosphonates induce BONJ more frequently, but scientific evidence tends to support the prevailing notion that the use of zoledronate carries the greatest risk^{4,18}. Our cases confirm the data reported by Dannemann *et al.*¹⁷, suggesting that the most commonly reported cases are associated with intravenous bisphosphonate treatment and only a small number of cases of jaw osteonecrosis after continued oral use of alendronate (Fosamax^R) to treat osteoporosis. Sook-Bin Woo *et al.*¹⁰ report that 94% of BONJ patients received pamidronate or zoledronate intravenously, and 6% of them took oral bisphosphonates as treatment for osteoporosis or Paget's disease.

The presence of actinomyces colonies was not confirmed in the present series, although they were found to be the most common microbiological finding¹⁷.

In all three cases, the pathology investigation ruled out diagnosis corresponding to the principal condition treated with bisphosphonates. It consistently found necrotic bone surrounded by bacteria but not invading it, thus also excluding the possibility of osteomyelitis. Three main histologic patterns were identified in BONJ patients: 1) areas with active acute inflammation, characterized by predominance of soft tissues, inflammatory infiltrate, acellular necrotic debris, thin-walled and dilated blood vessels, and intensely basophilic bone spicules with scalloped borders showing prominent bone resorption; 2) areas characterized by predominance of bony structures showing wide acellular necrotic sequestra and large, scalloped haversian canals containing inflammatory cells; and 3) non-necrotic areas contained larger amounts of bone, showing increased trabecular thickness, inter-osteonic bone deposition and smaller and fewer haversian canals. Also, lamellar bone from treated patients was composed of bigger osteones containing larger osteocytes. Two different types of newly-formed woven bone, mainly showing centrifugal spatial orientation, were easily detectable in these areas. Osteoclast-like cells detected in inflammatory areas from treated patients were small and contained few nuclei, but they were rare to absent in non-necrotic bone from the same patients¹⁹.

The patients in this study received intravenous bisphosphonates for 18 to 42 months. Bamias *et al.*⁴ believed that there was a strict correlation between the duration of bisphosphonate treatment and the manifestation of jaw necrosis. They found that the median time of exposure to bisphosphonates for patients with BONJ was 39.3 (11 to 86) months, and for patients without BONJ 19 (4 to 84.7) months. The authors report that the cumulative risk of BONJ development increased above 1% after 12 months of treatment and up to 11% at 4 years. They also found the risk to depend on the type of bisphosphonate used; for zoledronate it was 1% within the first year of treatment and up to 21% at 3 years, while for pamidronate it was 0% for the first 2 years, increasing to 7% after 4 years. Corso *et al.*¹⁸ have defined the following time periods for the development of BONJ in relation to the type

of bisphosphonate: treatment with pamidronate leads to necrosis not earlier than 23 months after initiation of therapy; this period is not shorter than 28 months with zoledronate treatment; after combined use of pamidronate and zoledronate, necrosis could not be observed earlier than 43 months. Badros *et al.*²⁰ found that the risk of developing BONJ increased by 57% *per* each year after diagnosis of multiple myeloma was made and bisphosphonate treatment initiated.

In two of the patients presented, BONJ occurred after dental extractions, while in the third one it was due to pressure-induced injury by a new complete denture. Literature review showed that cases of BONJ preceded by dental procedures prevailed over cases of the so called spontaneous BONJ^{4,20}, with 33% to 86% of all cases developing after different dental procedures¹⁴.

The patients presented in this report were aged 73, 54 and 78 years. It has been reported that the risk of developing BONJ increases by 9% for each decade of life²⁰.

Different authors have not reached agreement on whether bisphosphonate treatment should be stopped after osteonecrosis of the jaws has been diagnosed. Marx *et al.*²¹ suggest that continuation of bisphosphonate treatment in oncology patients should be discussed with the oncologists and the benefit to risk ratio assessed in view of the long half-life (more than 10 years) of bisphosphonates. Dunstan *et al.*²² believe that bisphosphonate therapy should be discontinued. In our opinion, discontinuation of bisphosphonate treatment is not justified in patients with metastatic cancer. The AAOMS is paper marked the treatment goals: control of pain, control of secondary infection, and prevention of extension of lesion and development of new areas of necrosis³.

One of our patients was treated by lesion debridement and flap coverage with local tissues. Most authors^{23,24} recommend that this approach should be avoided because of the risk of necrotic involvement of new bone areas. It is, however, our preferred method in case of relatively small necrotic area and presence of sufficient adjacent soft tissues without inflammatory infiltration. The other two patients were treated with periodic debridement of necrotic areas leaving exposed bone and antibiotic application, for reduction of symptoms. This is a treatment protocol advocated

by Graziani *et al.*²⁵, who, however, did not exclude the possibility for sequestrectomy and resection in some cases. The AAOMS position is that surgical treatment should be delayed if possible, and the extraction of symptomatic teeth within exposed, necrotic bone should be considered since it is unlikely that the extraction will exacerbate the established necrotic process³. In the literature, the opinion prevails that aggressive surgical treatment is counter-productive, results in worsening of the condition, and therefore should be avoided^{15,23,24,26}. We recommend early removal of all bone surfaces with macroscopic necrotic appearance with or without flap coverage. Nastro *et al.*²⁷ emphasize that antibiotics could not penetrate necrotic tissues and hence should be only used to influence cellulitis in neighboring tissues. Our results confirmed this opinion as evidenced by disappearance of pain and signs of inflammation at follow-up examinations 1 month after the surgery and after systemic antibiotic treatment.

Conclusion

The proven benefits of bisphosphonates have resulted in their widespread use in certain patient groups in Bulgaria too. Consequently, this has led to the development of specific complications such as BONJ. The present case series comprises only three patients, but the number of cases diagnosed with BONJ in Bulgaria will increase with increasing awareness and more common and prolonged use of bisphosphonates. Despite the relatively short follow-up periods, the results of the present study made us believe that early detection and minimally invasive surgical treatment of BONJ in conjunction with antibiotic medication (cephalosporin-type for 7 to 10 days intravenous or penicillin-type for at least 20 days) ensure the best therapeutic results.

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Sažetak

OSTEONEKROZA ČELJUSTI UDRUŽENA S BISFOSFONATIMA – TRI PRIKAZA SLUČAJA I PREGLED LITERATURE

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Teška komplikacija terapije lijekovima koji sadrže bisfosfonate poznata je kao osteonekroza čeljusti udružena s bisfosfonatima. Prikazuju se tri bolesnika s osteonekrozom čeljusti udruženom s bisfosfonatima i to su zasad jedini opisani slučajevi ove bolesti u Bugarskoj. Dvoje bolesnika imalo je izloženu nekrotičnu kost mandibule, dok je u trećeg bila zahvaćena maksila. Bolesnici su bili liječeni zoledronatom, u dva slučaja zbog metastatskog raka prostate, a u trećem slučaju zbog metastatskog endometrioidnog karcinoma, i svi su bili podvrgnuti kirurškom zahvatu. Kod jednog bolesnika primijenjen je konzervativni kirurški debrideman, tj. uklanjanje samo nekrotičnog tkiva, uz primarno zatvaranje rane. U drugih dvoje bolesnika primijenjen je konzervativni kirurški debrideman i lokalna medikamentna terapija bez zatvaranja rane. Svi bolesnici primili su sistemsku antibiotsku terapiju. Tijekom razdoblja praćenja od 3 do 12 mjeseci nisu zabilježeni nikakvi znaci progresije bolesti. Raspravlja se o kirurškom pristupu primijenjenom u ovoj studiji u odnosu na etiopatogenezu, prevenciju i liječenje osteonekroze čeljusti udružene s bisfosfonatima.

Ključne riječi: Osteonekroza – kirurgija; Bolesti čeljusti, kemijski uzrokovane; Bisfosfonati – štetni učinci; Kirurški postupci, operacijski

