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Medication-related osteonecrosis and actinomycosis – coincidence or connection?

Osteonekroza polekowa i promienica – przypadek czy związek?

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ABSTRACT

Antiresorptive drugs (ARD), including bisphosphonates, monoclonal antibodies, SERMs and others, are widely used in treatment of various bone diseases, such as osteoporosis, metastatic bone disease, osteogenesis imperfecta, Paget's disease. These medications work by inhibiting bone resorption, and as a result increasing bone strength and preventing fractures. Although their use is associated with many clinical benefits, there've been cases of developing medication-related osteonecrosis of the jaw (MRONJ). While the pathogenesis of MRONJ remains incompletely understood, it is believed to result from a disruption in bone remodeling process, specifically the inhibition of osteoclast function. Moreover, infections caused by Actinomyces spp. have been implicated in the development of MRONJ, although their role in the disease remains unclear. This review brings out connection between ARDs, bone remodeling and oral microbiology, providing a comprehensive overview of the current understanding of MRONJ and its clinical implications.

Keywords: antiresorptive drugs, MRONJ, actinomycosis.

STRESZCZENIE

Leki antyresorpcyjne (ARD), w tym bisfosfoniany, przeciwciała monoklonalne, SERM i inne, są szeroko stosowane w leczeniu różnych chorób kości, takich jak osteoporoza, przerzutowa choroba kości, osteogenesis imperfecta, choroba Pageta. Ich działanie polega na hamowaniu resorpcji kości, co w rezultacie zwiększa wytrzymałość kości i zapobiega złamaniom. Chociaż ich stosowanie wiąże się z wieloma korzyściami klinicznymi, odnotowano przypadki rozwoju martwicy kości szczęki związanej z lekami (MRONJ). Podczas gdy patogeneza MRONJ pozostaje nie do końca poznana, uważa się, że wynika ona z zakłócenia procesu przebudowy kości, w szczególności z zahamowania funkcji osteoklastów. Ponadto z rozwojem MRONJ zostały powiązane zakażenia wywołane przez *Actinomyces spp*., chociaż ich rola w tej chorobie pozostaje niejasna. Niniejszy przegląd uwypukla związek między ARD a przebudową kości i mikrobiologią jamy ustnej, zapewniając kompleksowy przegląd aktualnej wiedzy na temat MRONJ i jej klinicznych implikacji.

Słowa kluczowe: leki antyresorpcyjne, MRONJ, promienica.

Introduction

Antiresorptive medications are important treatment options for preventing skeletal events and prolonging survival in a variety of bone diseases, including malignancies, osteoporosis, Paget's disease, and metastatic bone disease such as multiple myeloma, breast, lung, and prostate cancer. Despite the great clinical benefits, cases of medication-related osteonecrosis have been reported. It has been found that most reported cases involve the cranium and facial bones rather than the long bones, making these patients particularly challenging for the dentist.

Oral cavity microbiome

Diverse microbal communities are housed in the oral cavity, including bacteria, viruses, archaea and microeukaryotes. It is a highly dynamic environment of an advanced ecology, with specific non-shedding dental surfaces facilitated by complex biofilm communities. The oral cavity is not only characterized by distinct microbes, but also by in-

terfacing with the immune system and constant environmental changes. These include the flow of saliva, nutrition, masticatory forces. What is more, those are shaped by multiple factors: host's genetics, oral hygiene, medications, and many more. Dental and periodontal diseases can be easily developed in such a dynamic ecosystem. Oral microbiome's shape changes throughout life – while sterile until birth, infant's oral cavity is shaped in a similar way to their mothers after the delivery. In later stages, the diversity is shaped by the eruption of primary teeth, dietary changes, smoking, alcohol, and then decreases with age. The decrease is connected to higher rates of periodontal disease, systemic diseases (cardiovascular, cancers, Alzheimer's) and medication intake [1, 2].

Since 1700s over 700 species of oral microbes have been isolated and characterized [according to Human Oral Microbiome Database]. Bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, *Streptococcus mutans*, *Aggregatibacter actinomycetemcomitans* were, among others, described as key pathogens in the development of periodontal disease and caries. Over the time, microbial subtypes have specialized to reside in different sites, such as dental plaque or dorsal surface of the tongue. A growing number of infections, such as HPV or Epstein-Barr virus infection have been associated with oral cancers. Furthermore, some fungal infections (ex. C. albicans), were present in patients with oral squamous cell carcinoma. Previously mentioned *P. gingivalis* and *A. actinomycetemcomitans* have been associated with Alzheimer's disease, rheumatoid arthritis, colorectal cancer and more [1, 2].

Antiresorptive drugs

Antiresorptive drugs (ARDs) are widely used by patients suffering from osteoporosis, bone metastatis, osteogenesis imperfecta and many other bone-related diseases. Despite mechanism differences among variety of ARDs, their mutual aim is to increase bone strength and prevent it from fracturing. There are five most used antiresorptive agents: bisphosphonates, monoclonal antibodies, calcitonin, estrogens and selective estrogen receptor modulators (SERMs) [3]. The most used are bisphosphonates with nitrogen group, such as zolendronate, pamidronate, alendronate. Their course of action is to attach to hydroxyapatite binding in the bone, and when osteoclasts begin the resorption of the bone that is impregnated with BPs, BPs are impairing the action of osteoclasts by inhibiting progenitor development and recruitment. They also promote the apoptosis of osteoclasts. Both bisphosphonates and monoclonal antibodies such as denosumab are considered first-line drugs for osteoporosis [4]. Denosumab, which is fully human monoclonal antibody (IgG2) directed against RANKL, binds to RANKL with strong affinity and specificity, thereby preventing the activation of its receptor (RANK) on the surface of osteoclast precursors and osteoclasts. Preventing RANKL/RANK binding inhibits osteoclast formation, function and survival thereby suppressing cortical bone and trabecular bone resorption [5]. Selective estrogen receptor modulators (SERMs) and estrogens are mostly targeting osteoporosis and hormone-responsive conditions like breast cancer. SERMs, such as raloxifene and tamoxifen, act by selectively modulating estrogen receptors. They are acting as estrogen agonists or antagonists depending on the tissue, they promote bone density by inhibiting bone resorption while reducing risks of estrogen-sensitive cancers like breasts cancer. Estrogen acts antiresorptive because of its impact on RANKL/RANK/OPG system. It also decreases production of proresorptive cytokines and directly impairs osteoclasts [4, 6, 7]. Calcitonin also reduces bone resorption, binding with osteoclast by its calcitonin receptor and interfering with secretion of proteolytic enzymes [4]. It causes osteoclasts number to decrease. On the contrary, calcitonin deficiency can cause increased bone formation [8].

Bisphosphonate-Related Osteonecrosis of the Jaws/Medication-related Osteonecrosis of the Jaw

The first case of Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ) was described by Marx [9] in the early 2000s in a study of non-healing exposed bone in the maxillofacial region of a patient treated with bisphosphonates. BRONJ is a rare, severe disease whose exact cause is unknown [10,11]. The American Association of Oral and Maxillofacial Surgeons (AAOMS) defines it as "The presence of exposed jawbone, or bone that can be probed through an intraoral or extraoral fistula, for at least 8 weeks, in a patient with a history of antiresorptive and/or antiangiogenic therapy, and in the absence of previous radiation therapy to the head and neck" [12].

Due to the increasing number of cases of osteonecrosis of the jaw associated with medications other than bisphosphonates, such as antiresorptive (denosumab) and antiangiogenic drugs, mTOR inhibitors, tyrosine kinase inhibitors, and most recently immunomodulators, the AAOMS Special

Committee recommended in 2014 a change in nomenclature from BRONJ to the term medication-related osteonecrosis of the jaw (MRONJ) [13, 14].

Actinomycosis

Actinomycosis is a rare, subacute or chronic granulomatous infection caused by gram-positive anaerobic *Actinomyces species*. The *Actinomyces genus* of the family *Actinomycetaceae* (which include the genera *Actinomyces*, *Nocardia* and *Rhodococcus*) comprises more than 40 species that have been officially registered [15]. To date, 26 individual *Actinomyces spp*. have been reported associated with clinical infections in humans, with *A. odontolyticus*, *A. meyeri*, *A. gerencseriae* and *A. israelii* accounting for more than 90% of these infections [16], with the latter accounting for up to 75% of human disease [15].

Actinomyces are endogenous flora of the mouth and gastrointestinal tract. They are usually of low virulence and enter deeper tissues through damaged mucous membranes of the oral cavity, midpharynx and gastrointestinal tract or by aspiration. The most common form, cervicofacial actinomycosis, is often associated with trauma, dental procedures, molar eruption, oral surgery, or tooth infection, particularly in patients with decreased immunity or poor oral hygiene. There have been some associations of cervicofacial actinomycosis with osteomyelitis and osteonecrosis, especially BRONJ [17]. Diagnosis may be difficult due to the presence of mixed bacterial flora and the need for long-term cultivation of *Actinomyces* under anaerobic conditions.

Discussion

Osteonecrosis of the jaw (ONJ), depending on the source, occurs more frequently in the mandible than in the maxilla (65% mandible, 28.4% maxilla, 6.5% both mandible and maxilla, 0.1% other locations) [18,19]. According to the literature, the incidence among users of antiresorptive drugs ranges from 0.7% to 18% [20]. The incidence of ONJ is directly related to the primary disease and the method of drug administration. In patients treated for osteoporosis, the incidence of ONJ ranges from 1.04 to 69 per 100,000 patients/year for oral administration and from 0 to 90 per 100,000 patients/year for intravenous administration [18]. Based on different national studies, the incidence of ONJ in patients with osteoporosis receiving BP drugs ranged from 0.01% to 0.07% [21]. Based on these epidemiological data, cases of ONJ in patients with osteoporosis appear to be very rare. There is significant difference of ONJ incidences in cancer patients, particularly treated with i.v. bisphosphonates, ranging from 0 to 12,222 per 100,000 patients/years [17]. It may be closely related to the malignancy of the tumor, other drugs used in cancer treatment, and significantly higher doses of drugs used in cancer compared to those used in osteoporosis.

Since the first reported case of bisphosphonate-related ONJ (BRONJ) in 2003 [9], an increasing number of research articles have been published showing similar complications associated with other antiresorptive drugs.

Although MRONJ/BRONJ is still incompletely understood, it is believed to originate from a defect in bone remodeling, when sensory osteocytes signal to osteoblasts and osteoclasts to, in response to stimuli, respectively form and resorb the bone. Through gap junctions and signals, osteocytes communicate with each other as well as with osteoblasts and osteoclasts. Osteocytes are connected within fluid cavities, and respond to stress induced by mechanical loading. They do that by altering gene expressions through relayed signals, changing the expression levels of COX-2, RANKL and osteoprotegerin. Osteoclasts differentiation is regulated by RANK which activates RANKL. The integrity of the bone is maintained by the intracortical remodeling process, which guarantees the replacement of micro-damaged areas and nonviable osteocytes. Furthermore, osteoclast precursor cells are called upon by compounds released after osteocyte's death. They initiate the damaged bone's resorption process. The fact that pharmacological agents inhibit osteoclasts' function suggests the central role of osteoclasts as disease initiators [22, 23].

The bone is a dynamic tissue that undergoes constant remodeling to maintain a healthy skeleton. It is well known that the mandible and maxilla have greater bone turnover than other skeletal bones (e.g., 10–20 times greater than in the ilium) [24, 25] due to the constantly applied pressures associated with chewing. This is directly related to the higher bone vascularization, which in turn allows for higher concentrations of antiresorptive drugs in the bone tissue in this area. Additionally, oral mucosa is thin and susceptible to damage, which facilitates bacterial infection of the exposed bone.

The growing number of cases presenting linkage between BRONJ (the Bisphosphonate-Related Osteonecrosis of the Jaws) and Actinomyces resulted in lots of studies trying to define this correlation. Both actinomycosis and BRONJ can be initi-

ated by some sort of injury to the bone – such as tooth extractions or other forms of surgical procedures in this area.

Russmueller et al. [11] investigated a possible role of Actinomyces spp. in the pathogenesis of MRONJ. Biopsies of necrotic bone collected during surgical treatment of MRONJ were evaluated for the presence of Actinomyces spp. From 111 patients suffering from histologically-confirmed MRONJ, Actinomyces spp. were detected in 99 cases (89%) by histology and in six further patients by microbiological culture.

Brody et al. [26] report that in the literature, the proportions of MRONJ samples with Actinomyces present vary drastically, from 12% to 100%. This difference might be caused by whether Actinomyces were a random finding or specifically searched for during staining. This concludes that much lower rate of Actinomyces in MRONJ in some cases might be related to false negative results. Their study focused on re-evaluation of 112 samples of patients treated with bisphosphonates from the archives of Semmelweis University. During the first routine histological evaluation, 102 samples were reported as Actinomyces negative. 95 out of the 102 previously negative samples were found to be positive during the triple staining re-evaluation. In total, 105 out of the 112 samples were found to be Actinomyces positive (93.75% compared to 8.93% in the original evaluation).

Schipmann et al. [27] analyzed 51 cases of BRONJ, by searching for Actinomyces colonies in the necrotic bone specimens. Actinomyces were found in and on the necrotic bone in 86% of the cases (n = 44). What is more, among Actinomyces-negative specimens, 7 were found to show signs of inflammatory reaction.

Ogura et al. [28] reviewed CBCT imaging and histopathological characteristics of MRONJ and osteoradionecrosis. Not only did they evaluate the presence (or absence) of necrotic bone, osteoclasts and inflammation, but also the presence of Actinomyces. In 9 out of 10 cases, various Gram (+) and Gram (-) bacteria were found, while Actinomyces was found in 6 out of 10 cases.

A different microbiological approach was taken in research conducted by Aftimos et. al. [29] The study observed 18 necrotic lesions related to BRONJ and inspected them for fungi instead of bacteria. 100% of the examined specimens showed the presence of the fungi in BRONJ. However, as the authors admit, the results might be misleading as some fungi are nonpathogenic. On the other hand, determining the nature of those microorganisms may change the course of BRONJ treatment by adding a specific antifungal treatment.

Conclusion

Antiresorptive drugs are the most used pharmacological treatment for osteoporosis and reduce the risk of all types of fragility fractures. Evidence linking the development of MRONJ to the use of antiresorptive drugs in the context of osteoporosis is limited.

Many clinical factors have been considered in the pathogenesis of ONJ, particularly dental procedures such as tooth extraction, periodontal disease, and denture trauma. It is important to understand that not all dental complications can be avoided. However, the incidence of dental complications can be significantly reduced with careful evaluation before treatment.

Despite many research featuring Actinomyces colonies in the biopsies from MRONJ patients, it is still unclear, if Actinomyces are playing a significant role in pathogenesis of MRONJ, or their presence in necrotic bone is simply post-necrotic [11].

It is important to remember the risk of developing MRONJ is small compared with the benefits of bisphosphonates or other antiresorptive drugs. So far, no evidence-based study has demonstrated efficacy of bisphosphonate drug holiday in preventing MRONJ [30].

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Conflict of interest statement

The authors declare no conflict of interest.

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