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Case Report

RANK-Ligand inhibitor associated osteonecrosis of the jaw

RANK-Ligand Inhibitor-assoziierte Osteonekrose des Kiefers

Abstract

Osteonecrosis of the jaw may be caused by many different triggers. One of them is described to be the drug or medication related osteonecrosis of the jaw. Since many years bisphosphonates induced the dreaded diagnosis. Recently a drug named denosumab is reported to show similar effects on the jaw. In this case report we present a RANK-Ligand inhibitor associated osteonecrosis of the lower jaw and discuss the lights and shadows of this newly introduced drug.

Keywords: RANK-Ligand inhibitor, denosumab, osteonecrosis, jaw, bisphosphonates

Zusammenfassung

Die Osteonekrose des Kiefers kann durch verschiedene Auslöser verursacht sein. Einer dieser Auslöser wird als die Medikamenten-assoziierte Osteonekrose des Kiefers beschrieben. Seit mehreren Jahren induzieren Bisphosphonate die gefürchtete Diagnose. Kürzlich wurden ähnliche Auswirkungen durch Gabe des Arzneimittels Denosumab beobachtet. Anhand des Fallberichtes präsentieren wir eine RANK-Ligand Inhibitor assoziierte Osteonekrose des Unterkiefers und erörtern die Licht- und Schattenseiten des neuartigen Medikaments.

Schlüsselwörter: RANK-Ligand Inhibitor, Denosumab, Osteonekrose, Kiefer, Bisphosphonate

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Introduction

Many patients suffer from bisphosphonate related osteonecrosis of the jaw (BRONJ). Bearing in mind increasing administration of bisphosphonates (BPs) worldwide, the peak is not yet reached [1]. BPs are drugs widely used in the treatment of various bone related disorders such as osteoporosis, multiple myeloma and bone metastases [2].

Chemically, BPs are small molecular size stable analogues of natural inorganic pyrophosphates, with a carbon atom replacing the oxygen atom that connects the two phosphates [3]. They are classified as aminobisphosphonates or non-aminobisphosphonates and administered orally or intravenously. The mechanism of action concerns apoptosis of osteoclasts, decreased resorption activity and hence limited bone remodeling [4].

RANK-Ligands (Receptor Activator of Nuclear Factor Kappa-B Ligand) are produced by osteoblasts and promote differentiation of osteoclasts by binding to RANK-receptors located on these. A new drug group, namely denosumab (Prolia®), acts by attaching to RANK-Ligands in order to prevent binding of the complex to RANK-receptors resulting in an impaired function of osteoclasts. While the pharmaceutical aim is the same as for BPs, the way of action differs [5]. In general, the area of indication is similar to widely distributed BPs [6], [7].

Denosumab was approved by European Medicines Agency in May 2010 for the treatment of osteoporosis of women in postmenopause and osteoporosis in men caused by hormone therapy due to prostate cancer [8]. The US Food and Drug Administration followed that approval in June 2010 [9] and extended the therapeutic field for osteoporosis in men independent of hormone therapy in September 2012, which is still outstanding in European Union [10].

Case description

A 74-year-old edentulous woman with osteoporosis and fibromyalgia complained about growing pressure pain of the mandible following extraction of the lower anterior teeth and insertion of mucosa supported complete denture 6 months ago. Her medical history revealed 6 time administration of denosumab (Prolia® 60 mg) subcutaneously over the past 2.5 years. Fibromyalgia was

treated with decortin. While intraorally no dehiscence was detected (Figure 1), a panoramic view indicated irregular bone morphology especially in anterior mandible (Figure 2) compared to preoperative imaging 10 months ago (Figure 3). A CT scan illustrated the whole extent (Figure 4). A RANK-Ligand inhibitor (denosumab) associated osteonecrosis of the mandible was diagnosed and reminded us of known BP effects on the jaw. Due to missing dehiscence she was treated conservatively with sultamicillin and prosthesis leave for 2 months with slight improvement of complaints. On the other hand with respect to the great extent of the osteonecrosis, we clarified the potential need of microvascular free flap for reconstruction.

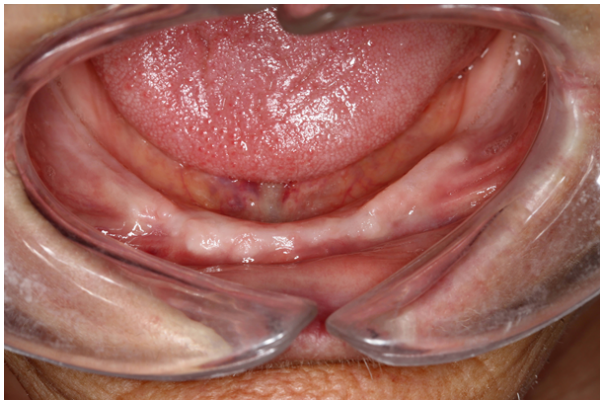

Figure 1: Intraoral illustration of lower jaw with absence of any dehiscence

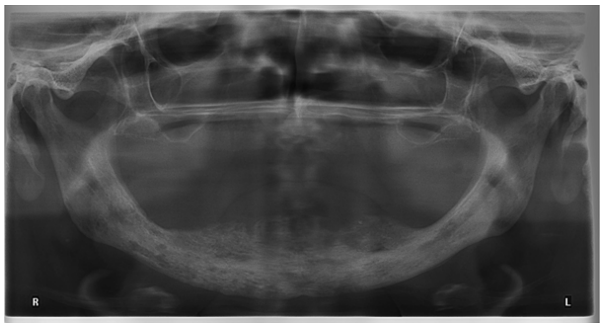

Figure 2: Panoramic view reveals edentulous site after extraction and disturbed presentation of mainly anterior part of the mandible

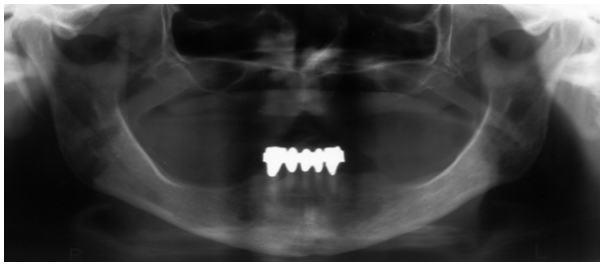

Figure 3: Panoramic pre-extraction view with remaining anterior teeth 10 months ago

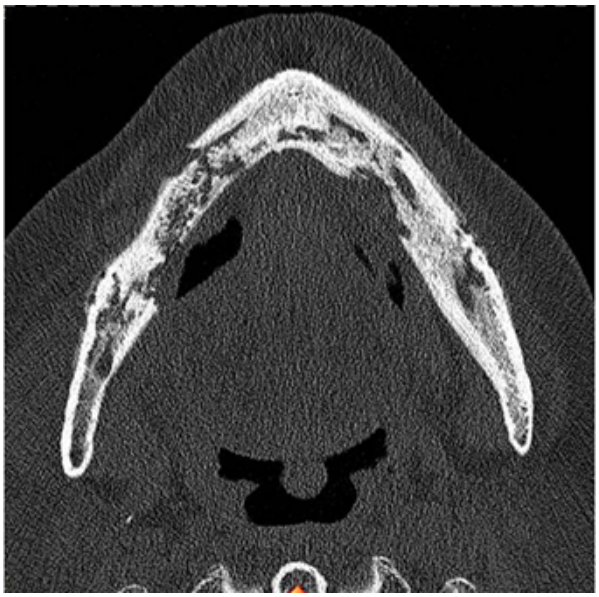

Figure 4: Finally CT scan showed up whole extent of osteonecrosis

Discussion and conclusion

About 10 years after the first reported and published cases of BRONJ [11], [12], a new drug group seems to be associated with similar or even more serious impact. Denosumab is a human monoclonal antibody and inhibits osteoclast differentiation and proliferation. It has shown great clinical results with even better bone density values compared to BPs [13], [14]. However, the costs are many times higher than for BPs. But due to higher and improved bioavailability, administration of denosumab would be sufficient subcutaneously every 6 months.

In contrast to BPs, half-life is not supposed to be several years. Denosumab's median half-life period amounts 26 days and could not be detected in more than half of probands after 6 months. This fact could be beneficial with respect to necessary dentoalveolar surgery. While that kind of treatment should be performed necessarily before BP uptake, denosumab could theoretically allow operation even after administration requiring absence of the drug for several months.

Nevertheless, above presented case suggests that the RANK-Ligand inhibitor is able to harm the jaw seriously in short period of time. Further studies have to investigate possible angiogenesis inhibition and soft tissue toxicity as reported for BPs [15], [16]. That is why we favor to treat conservatively if possible at the moment. Surgical procedures should be held limited and gentle to the periosteum as for BRONJ.

Notes

Competing interests

The authors declare that they have no competing interests.

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