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Consolidation of Tumorous Mandibular Ramus Defect During Denosumab Treatment for Rapidly Progressive Metastatic Breast Cancer

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Abstract. *Background: Pharmacological inhibition of osteoclast activity is an essential component of oncological therapy for patients with bone metastases. In rare cases, medication-related osteonecrosis of the jaws (MRONJ) is observed. MRONJ can cause bone defects not inferior to primary or metastatic jaw neoplasms. Oral examination of patients on osteoclast-inhibiting medication aims to identify risk factors at an early stage and to initiate therapy. The current focus on osteoclast-inhibiting drugs in the maxillofacial region is MRONJ. Effects of the substances other than MRONJ are rarely reported. Case Report: The female patient with metastatic breast cancer had developed extensive osteolysis of the mandibular ramus at the time of initial diagnosis. The patient was treated with denosumab. Seven months later, a significant reduction in the mandibular osteolytic zone was recorded. However, known bone metastases from other sites had increased in size during multimodal therapy, and further metastases were recorded. Conclusion: Jaw metastasis can shrink under denosumab therapy.*

Pharmacologic inhibition of osteoclast activity is an essential oncologic tool for treating bone metastases (1). In addition to bisphosphonates, other drugs are now approved and in widespread use whose common metabolic effect is to slow down or even stop bone degradation (2). It is not uncommon for these substances to be used on a long-term basis, to have an impressive effect on bone stability and greatly improve the patients' quality of life (1). However, the osteoclast-inhibiting drugs may have severe adverse effects on the integrity of the jaws in some patients. First described in patients under bisphosphonate (3) and later observed for other substances with this osteologic effect (4), necrosis of the jaws of varying degrees may occur (5). These lesions are currently defined under the umbrella term medication-related osteonecrosis of the jaw (MRONJ). Therapeutic needs can range from treatment for circumscribed necrosis, pathological jaw fracture up to loss of the entire bone. Dental and surgical care of the patients has a high value in prophylaxis and monitoring of patients under anti-osteoclastogenic therapy (6, 7). Typical signs of MRONJ are non-healing wounds after dental treatment or non-ossifying bone following tooth extraction (8) or spontaneously occurring and non-healing mucosal defects with consecutive jaw necrosis (9, 10). The use of osteoclast inhibitors for the treatment of jaw metastases is not the focus of this medication. Application of inhibitors of osteoclasts is discussed for oral carcinoma invading the jaws (11). This report is intended to add to the knowledge about the spectrum of effects of osteoclast-inhibiting pharmaceuticals on the jaws in metastatic disease.

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Case Report

The 44-year-old patient was treated for metastatic breast cancer. The first contact with the patient in the outpatient clinic of the department of oral and maxillofacial surgery was because of the planned medication with Xgeva® (denosumab) for treatment of bone metastases. The patient was known to have breast carcinoma at the time of the initial examination. Dental status and oral risk factors were to be checked before the planned medication. Oral examination confirmed intact mucosa and well-maintained dentition. However, the panoramic view of the jaws showed osteolysis of the right ramus as an incidental finding. The bone defect was located at the level of the mandibular foramen (Figure 1A and C). At the time of the examination, the patient did

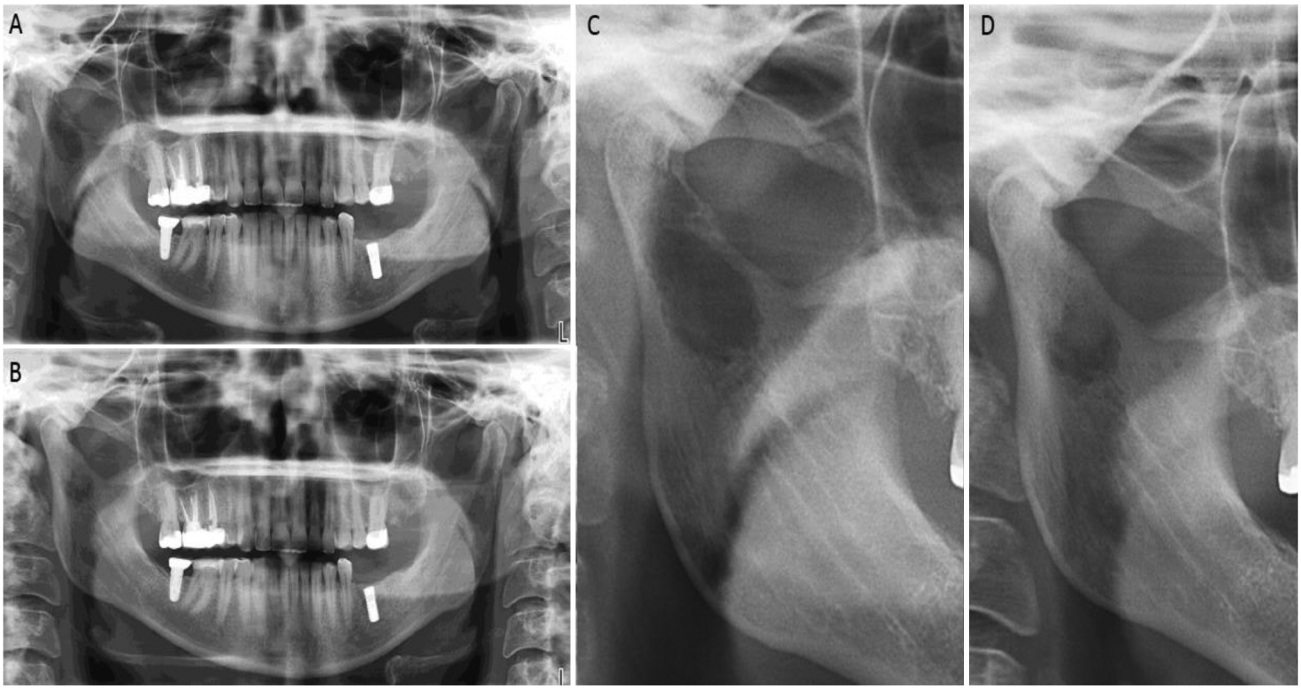

Figure 1. *Panoramic views of the jaws at the time of initial diagnosis (A) and seven months after chemotherapy (B). (A) The overview shows the extensive, indistinct osteolysis of the right ramus, which lies below the incisure and ends above the mandibular foramen. During seven months of treatment (B), the radiotranslucent region is reduced to the caudal area of the defect. (C) is a detail of Figure A and illustrates the tumor-typical radiotranslucency of the bone. (D) is a detail from Figure B and illustrates the consolidation of the lesion under therapy.*

not report any sensory disturbances of the mandibular nerve. In connection with the patient's disease, the finding was interpreted as a metastasis of the primary carcinoma. Surgical intervention was not performed because there was no fracture risk, and the patient was locally symptom-free.

Histology. Poorly differentiated, invasive breast carcinoma with axillary lymphogenic metastasis, undifferentiated (G3), Her2 positive tumor cells, nuclear positive estrogen receptor: 80%, nuclear positive progesterone receptor: 15%, proliferation rate of tumor cells (Ki-67): up to 50% (in hot spots).

Additional sectional imaging. Computed tomogram of the whole body revealed multiple distant metastases throughout the spine and in the pelvis, liver, and lungs. Re-evaluation of the spine CT carried out during the first staging of the patient showed part of the skull base on some sectional images. On these images, part of the right mandibular ramus could be assessed. The CT showed sharply defined vestibular osteolysis with loss of cortical bone in the area below the semilunar incisure (Figure 2A-C).

Treatment. The patient was treated with a combination of letrozole, gonadotropin releasing hormone agonist (GnRHa), and ribociclib. Adapted chemotherapy regimen used trastuzumab and pertuzumab following diagnosis of tumor progression four months later. Denosumab was immediately applied after primary diagnosis of the disease. Daily oral substitution of calcium and vitamin D3 were administered.

Course of disease. In the further course of the disease, the patient was examined again in the outpatient clinic seven months after having started denosumab medication. Oral findings were unchanged from the initial examination. However, panoramic view now disclosed a significantly reduced osteolytic zone of the ramus compared to the initial examination. Compared to the apparently non-tumorous bone, the radiopaque content of the bone lesion resembled an ossifying callus. Only in the caudal part of the defect still was visible a radio-translucency as already registered on initial examination (Figure 1B and D). The finding was confirmed in mandibular cone beam tomography CBCT (Figure 2D-F).

MRI clearly disclosed the different composition of both radiopaque structures, *i.e.*, bone and the re-calcifying zone. The callus-like ossification zone extended beyond the level of the cortical bone in a slightly arched shape, laid directly against the masticatory muscles, and was sharply demarcated to the soft tissues (Figure 3A-C). Muscle infiltration of the

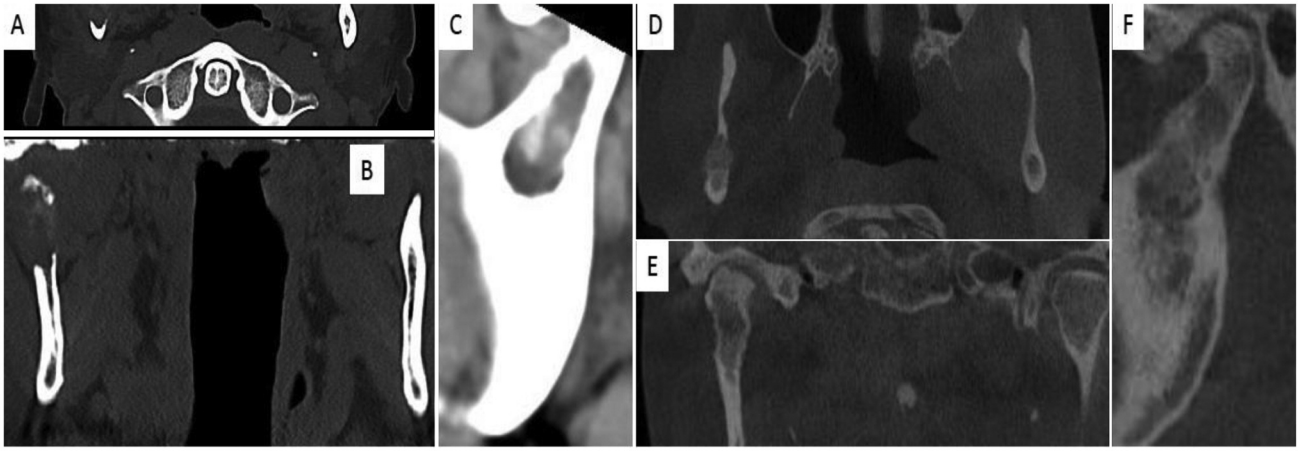

Figure 2. *Slice images of the jaws with computed tomography (A-C) and cone beam computed tomography (CBCT) (D-F) (cropped images). (A-C) The CT was taken at the time of the initial diagnosis and shows the skull base in the border area of the field of view. (A) The axial layer shows the incisure of both mandibular sides. The right side of the jaw has a sharply defined, bowl-shaped, bi-cortical osteolysis. (B) The vertical dimension of the osteolysis becomes clear in the coronal view. (C) In sagittal projection, the central defect is partially circumscribed by cortical bone. CBCT was performed seven months after chemotherapy. (D) The axial image shows the hyperdense filling of the bone defect. This filling has a suggested oval outline and a density like bone. (E) The coronal image reveals the irregular surface of the hyperdense defect filling. Compare the contour of the vestibular bone surface on MRI with the bone surface image on ultrasound in Figure 4. (F) The sagittal image shows the inhomogeneous hyperdensity within the defect filling.*

lesion could not be inferred from MRI. However, MRI revealed brain metastases (Figure 3D).

In addition, transcutaneous B-scan ultrasonography of the right cheek region, was performed. Parotid gland and masseter muscle showed a regular structure: there was no evidence of infiltration of the soft tissue. In typical fashion, total ultrasound reflection with distal ultrasound extinction occurred at the interface with the mandibular ramus. The reflection pattern was linear according to the shape of the bone surface in this area. However, at the site of the lesion, the linear reflection pattern was interrupted and replaced by a slightly wavy reflection pattern. No transmission was registered distal to ultrasound reflection in the defect area, that is, the total ultrasound reflection at the bone surface was registered over the entire ramus. The finding was interpreted as indication of re-calcifying ramus in the former defect area. Apparently, surface re-ossification was uneven at the time of examination. The smooth cortical side of the bone was not restored in the region of calcification. No vessels were depicted within the callus-like regenerate. A thin, continuous, homogeneously ultrasound-permeable layer was located between the ultrasound-impermeable bony defect region and the adjacent muscle (Figure 4).

Due to the new brain metastases that occurred during medical treatment, cranial irradiation including the base of the skull was planned. Exposure of the right ramus was included in the radiation field.

Discussion

The report describes the consolidation of extensive mandibular osteolysis during denosumab therapy in a case of breast cancer that had already metastasized to the bone at initial diagnosis. The finding of drug-related mandibular re-ossification is unusual for two reasons. First, the calcification was observed in a patient with radiological evidence of additional skeletal metastases on denosumab therapy. Second, medical attention to mandibular lesions under denosumab therapy usually focuses on the diagnosis of drug-associated mandibular necrosis.

Pharmacological effect of denosumab on bone in cancer therapy. Denosumab is a human monoclonal antibody that inhibits the formation, function, and survival of osteoclasts by binding to receptor activator of nuclear factor-kappa B ligand (RANKL), thereby reducing bone resorption in cortical and trabecular bone. Denosumab is approved in a lower dosage for the treatment of osteoporosis in postmenopausal women at increased risk of fracture and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fracture. In a higher dosage denosumab is indicated for the prevention of skeletal-related complications (such as pathological fractures) in adults with bone metastases due to solid tumors, *e.g.*, breast cancer (12). Denosumab significantly reduced treatment-related osteoporosis associated with breast cancer

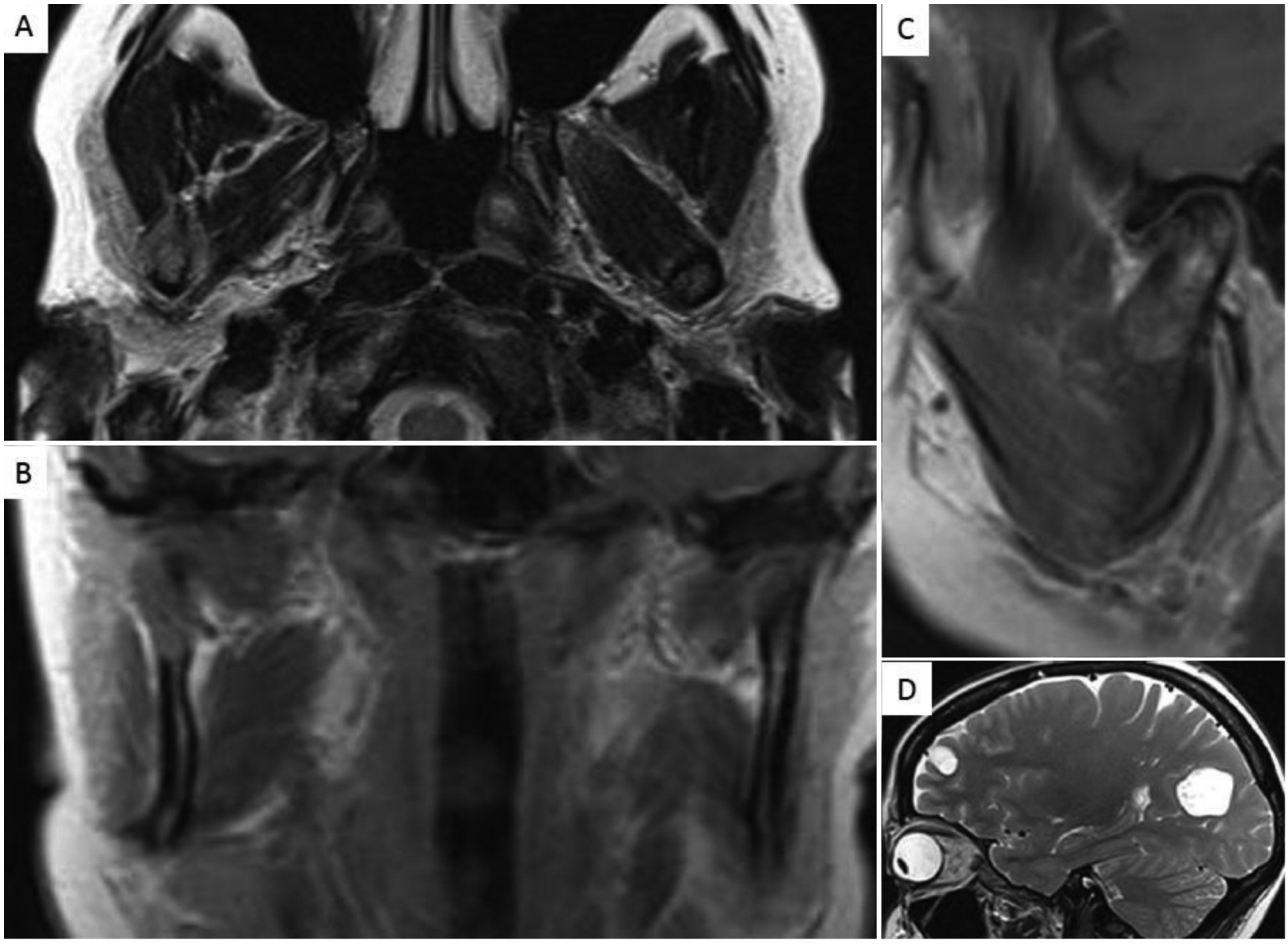

Figure 3. *MRI shows the sharp boundary of the lesion against the soft tissues in axial (A), coronal (B), and sagittal projections (C). (D) Brain metastases that developed during treatment.*

(13). However, this is an effect that can only be sustained with long-term medication. Pathological fractures after discontinuation of denosumab have been published (14). This rebound effect can be explained by the temporary binding of the protein to the specific osteoclast receptor (14, 15). In addition, the effects of the substance on bone preservation depend on calcium levels and thus on kidney function. In fact, there are doubts that a substance inhibiting osteoclasts can simultaneously promote bone formation. Rather, some authors consider medication(s) to prevent metastatic osteolysis and bone regeneration should start at different times and be based on different drugs (16, 17).

Some authors report that the correlation of decreased blood flow to the jaw and the development of necrosis of the jaw, which has been shown for bisphosphonates, has not been demonstrated for denosumab. The authors therefore hypothesize that the increased bone density of the jaws under denosumab is either limited to the cortical and not the cancellous bone or the effect is based on other, currently unknown factors (18, 19). The presented case demonstrates a calcification of the defect, which suggests a partial restitution of the bone in the panoramic view and only reveals the bone structure deviating from the radiological norm in the sectional images. The ossification mainly affects the cancellous bone. However, formation of bones and blood vessels are closely related (19).

In principle, the effect of other oncological drugs must be considered to explain recalcification of the defect. However, no clinically relevant osteogenic potential is known for the applied drugs. Rather, the drugs (aromatase inhibitors, hormone analogues, antibodies) are known to interfere with bone metabolism and can cause substantial bone loss (2, 20, 21).

Effect of denosumab on carcinoma cells. Some authors hypothesized the RANK inhibitor denosumab, in addition to inhibiting osteoclasts, can also have a direct effect on

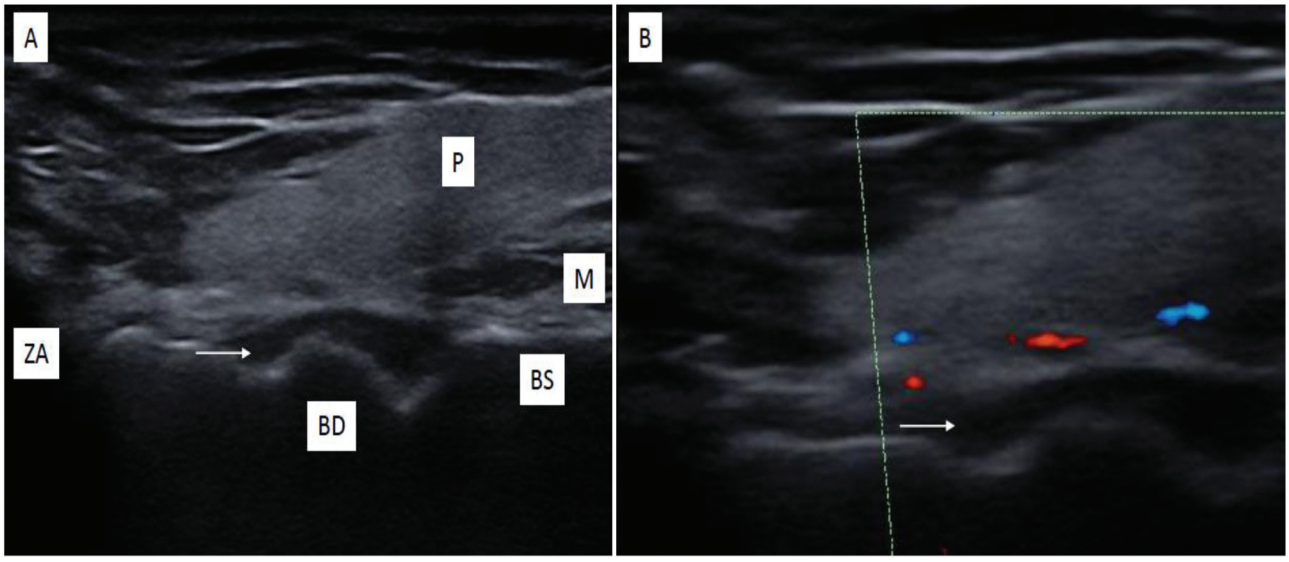

Figure 4. *Ultrasound image of the right cheek region (cropped images). Cranial is to the left in both figures. (A) The overview shows the parotid gland (P) with the masseter muscle (M) below. The complete reflection of the ultrasound at the unaffected bone surface produces a linear pattern in the area below the defect, confirming a smooth bone surface (BS). Further cranially and in the former bone defect (BD), the reflection pattern of the bone surface becomes slightly wavy, indicating the uneven distribution of ultrasound-reflecting structures. The left edge of the image shows the acoustic shadow created by the zygomatic arch (ZA). (B) The Doppler function of ultrasound reveals vessels within the gland. The calcified region has no representation of vessels. In both images, a slightly arcuate, thin, hypodense region separates the muscle from the bone surface (Arrow in A and B). Such hypodense boundary layers are often observed in mandibular callus formation.*

carcinoma cells (22). Therefore, it has been hypothesized that a second, direct anti-tumor effect could also be effective in preventing bone metastases or stopping bone resorption (22). Indeed, some authors have interpreted current studies on denosumab in metastatic breast cancer as evidence of a medication-related prolonged overall survival and prevention of tumor recurrences at all sites (12). However, in the present case multiple metastases developed in soft and hard tissues during denosumab treatment. Indeed, adjuvant denosumab does not improve bone metastasis-free survival in breast cancer (2).

Off-label use in different bone-related neoplasm. In addition to the treatment of osteoporosis, anti-osteoclastogenic drugs are used for treatment outside the original indication (23). Reports of previous use of denosumab in which new bone formation has been observed include giant cell granulomas and giant cell tumors (24, 25). It has been reported that denosumab supports the osseous regeneration of breast cancer bone metastasis in individual cases if the lesion is characterized by giant cell-like cells (26, 27). In both situations appositional bone growth was detected in patients, and it was hypothesized that the RANK inhibitor has a specific effect on giant cell-like osteoclasts. It has been suggested that the conspicuous cells were derived from monocytes (26). However, the drug effect in multilocular osteolysis of giant cell-containing lesions of the axial skeleton appears to be more static than regenerative (25). For the mode of action of denosumab, the binding pattern of the substance must be considered. In contrast to permanent binding of bisphosphonates to osteoclasts, denosumab is effective in the extracellular milieu and interacts with RANKL expressing osteoclasts and their precursors. Denosumab is not stored in the bone and is passed on to the bloodstream through the reticuloendothelial system within about 4 weeks to be further metabolized and excreted (14). Regarding the case presented, a permanent ossification of the former defect after possible discontinuation of the drug cannot be estimated.

MRONJ. Examinations of the oral cavity and facial skull of patients under osteoclast-inhibiting medication are primarily aimed at detecting wound-healing disorders that may lead to necrosis of the jaws if left untreated (7). The proportion of MRONJ patients among oncologic patients on this medication presently is poorly defined (28, 29). Based on meta-analysis of data from specialty clinics, prevalence is about 0.5 to 2.1% during the first year of application and increases up to 3.25% after three years (29). However, in one study, the proportion of jaw necrosis under denosumab in metastatic cancer was approximately 11.4% (mean administration time: 4 months, range=2-52 months, n=14/123) (28). In contrast, the mean

drug exposure duration of denosumab-associated osteonecrosis in another study was 3.4±1.9 years [range=1-8 years, n=26, male/female=14/12; (18)]. The information on the frequency in relation to the respective tumor type is different, possibly also due to different evaluation criteria when jaw necrosis is recognized as caused by the specific medication (8). Co-morbidities seem to favor the occurrence of MRONJ (30, 31). However, the radiological phenotype of MRONJ is not uniform (10). Superficial loss of the cancellous bone in the bony parts facing the oral cavity can be observed, but also diffusely distributed hypodensities within the entire bone. The association of the lesions with tooth-bearing jaw sections is evident in many cases (10). Recognition of the distribution pattern of MRONJ has generated the presumed pathogenesis of microtrauma in the gingiva or mucosa, which are used as ports of entry of microorganisms to the bone. Correspondingly, examination of the dental health of the patients and the scientific analysis of potential predictive oral factors of the disease are intensive (7).

The mandibular osteolysis of the present case differs from the predilected sites and radiological pattern of MRONJ. The indicated oval defect has no ossification islands at the time of initial diagnosis on panoramic view and is relatively sharply demarcated from the unaffected bone. The radiological picture - in connection with the patient's medical history – is typical for bone metastasis. Distant metastases to the jaw are rare and usually a bad prognostic sign (32).

Conclusion

The presented case deviates from the usual dental and maxillofacial surgical assessment of patients under osteoclast-inhibiting medication. At the time of the initial examination, the patient was known to have metastatic breast carcinoma with bone metastases. The indication for medication with denosumab was undisputed and first line therapy was initiated immediately. The consultative evaluation by the oral and maxillofacial surgery clinic was assessment of oral status. Mandibular bone defect was an incidental finding. The defect was without contact to oral cavity. In the further course of disease, this bone defect became significantly smaller under denosumab medication. This effect was demonstrated by adequate imaging to assess facial bone, *i.e.*, plain radiography and CBCT. However, the assessment of soft tissue infiltration by CBCT was not possible. Simultaneous MRI showed sharply demarcated, ossifying lesion at the site of former metastasis. Ultrasound imaging of the site made very likely a substantial ossification of the lesion.

In rare cases, re-ossification of tumor-associated mandibular osteolysis may be observed with denosumab. Medical practitioners and dentists should consider this phenomenon when interpreting mandibular calcifications with respect to the patient's history.

Conflicts of Interest

The Authors have no conflicts of interest regarding the work presented.

Authors' Contributions

Diagnosis and treatment of patients: all Authors; drafting of manuscript: REF; final approval of manuscript: all Authors.

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