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Case Report

Medication-Related Osteonecrosis of the Mandible Treated with Marginal Resection: A Case Report

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Abstract: The aim of this report is to present a successful combined surgical and pharmaceutical treatment in the highest stage of medicine-related osteonecrosis of the jaw (MRONJ). A 70-year-old man treated for metastatic prostate cancer concomitant with hypertension and diabetes presented due to the exposure of the jawbone. Initial imaging studies suggested MRONJ, and the biopsy did not confirm bone metastasis in the oral cavity. Marginal resection of the mandible was performed after the administration of antibiotics and anticoagulants. There was no recurrence of mandibular necrosis during the 3-year follow-up. MRONJ can develop covertly, with scanty clinical symptoms, and can be easily overlooked. Radical combined treatment may, in some cases, prevent further progression of the disease, which was successful in this case.

Keywords: MRONJ; osteonecrosis; zoledronic acid; zoledronate; case report

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1. Introduction

Medicine-related osteonecrosis of the jaw (MRONJ) is a spreading iatrogenic disease, which has been known about since 2004 [1–6]. The main risk factor for MRONJ is taking antiresorptive drugs, among which attention is paid to bisphosphonates (BP) [6–9]. In the treatment of osteoporosis, BPs, such as alendronate, risedronate, and zoledronate, are mainly used [10,11]. Other indications for the administration of BPs are, e.g., breast cancer, prostate cancer, and myeloma [6,12–15]. Another popular antiresorptive drug is denosumab; however, it is associated with a significantly lower incidence of MRONJ [8,16]. Other drugs that are listed as likely to increase the risk of MRONJ are based on vascular endothelial growth factor (VEGF) anti-angiogenic drugs, tyrosine kinase inhibitors, and immunomodulators [17,18].

The likelihood of developing MRONJ is increased by numerous general and local factors, the most important of which are tooth extraction, periodontal disease, chemotherapy, taking corticosteroids, and smoking [6,8,9]. The risk of developing MRONJ in the group of patients taking antiresorptive drugs ranges from 0.04% to 21.26%, which depends, inter alia, on the primary disease, which, in turn, determines the use of a particular drug, as well as its dosage [1,7,19]. Thus, the underlying diseases most strongly correlated with MRONJ are myeloma, osteoporosis or osteopenia, and breast cancer [1,6,8,12,20].

The 2014 American Association of Oral and Maxillofacial Surgeons (AAOMS) classification specifies the MRONJ risk group and disease stages from 0 to 3 [21]. In the cases of stages 1 and 2, i.e., local exposure of necrotic bone with or without infection symptoms, the classical conservative management strategies recommended in the above-mentioned AAOMS paper are slowly being replaced by surgical treatment [11,22]. Stage 3, a necrosis

with a range exceeding the alveolar process and/or affecting the surrounding tissues, requires surgical resection of the necrotic bone, and, in the absence of such a possibility, is replaced with palliative treatment [6,21,22]. The detailed diagnoses qualifying MRONJ to the most advanced Stage 3 are: (1) the extent of bone necrosis beyond the maxillary or mandibular alveolar process; (2) pathological fracture; (3) cutaneous fistula; (4) nasal or antral fistula; and (5) osteolysis reaching the base of the mandible or the floor of the maxillary sinus [21].

The aim of this report is to present the diagnostic process and successful treatment of a Stage 3 case of MRONJ according to the AAOMS classification [21].

2. Materials and Methods

This case report has been prepared in accordance with the CARE case reports guidelines [23].

2.1. Patient Information

A 70-year-old white male patient was referred from a dental outpatient clinic to a maxillofacial surgery hospital ward. The referring physician initially diagnosed the necrosis of the alveolar part of the mandible, and noted in the referral that the patient had previously been treated with bisphosphonates. On 24 February 2019, the patient was admitted to the Maxillofacial Surgery Department of the Hospital of the Ministry of Internal Affairs and Administration in Kielce. The patient was admitted conscious, with somewhat difficult logical contact, with slow reactions. The patient's family provided documentation on previous hospitalizations.

On the day of admission, the patient only complained about the exposed jawbone in the oral cavity. As part of the medical interview, the patient and his family reported a prior diagnosis of prostate cancer with bone metastases. Due to pharmacological castration resistance, chemotherapy based on docetaxel was initiated. The patient underwent the last cycle of chemotherapy at the turn of January and February 2018. Later, the patient was taking a bisphosphonate, zoledronic acid, at a dose of 4 mg, at intervals of 3–4 weeks from March to August 2018. The patient was unable to determine how long the mandibular bone had been exposed. He reported that the condition lasted for at least several weeks, and, due to the absence of pain, the exposure did not alert him. A later clinical examination indicated the possibility of necrosis initiation by the extraction of teeth in the anterior segment of the mandible. According to the data provided by the patient's family, it was determined that the teeth were extracted in five steps every 1–3 days in October 2018 on an outpatient basis, outside of our unit. After the procedure, amoxicillin with clavulanic acid and 0.12% chlorhexidine wash were prescribed.

A number of comorbidities were identified. The patient was treated for arterial hypertension and type 2 diabetes. In 2016, he underwent a myocardial infarction without ST segment elevation, and also underwent percutaneous coronary angioplasty. Drug-eluting stent was installed in the left anterior interventricular coronary artery. The patient had another myocardial infarction without ST segment elevation in August 2018. The medical history of allergies, alcohol, and tobacco use was negative. Therefore, the patient was classified as group III, according to the generally applicable American Society of Anaesthesiology (ASA) scale [24].

2.2. Clinical Findings

Clinical examination showed no cutaneous fistulas and normal mandibular mobility. Only the right medial bicuspid and left cuspid were found in the upper dental arch. The patient wore a partial upper denture. The mandible was toothless, and the patient reported that he did not use a lower prosthesis. Irregular gingival defects were found on the alveolar part of the mandible in the premolar, canine, and incisor regions. The shape of the mucosa appeared to correspond to abnormal healing following extractions of the lower left first molar, second bicuspid, cuspid, incisor, and lower right incisors, as well as second bicuspid.

Bared, non-bleeding, painless bone was visible within the gingival defects, which suggested a diagnosis of necrosis of the jaw. The gingival margins surrounding the exposed bone were inflamed. An intraoral image taken during the physical examination is shown in Figure 1.

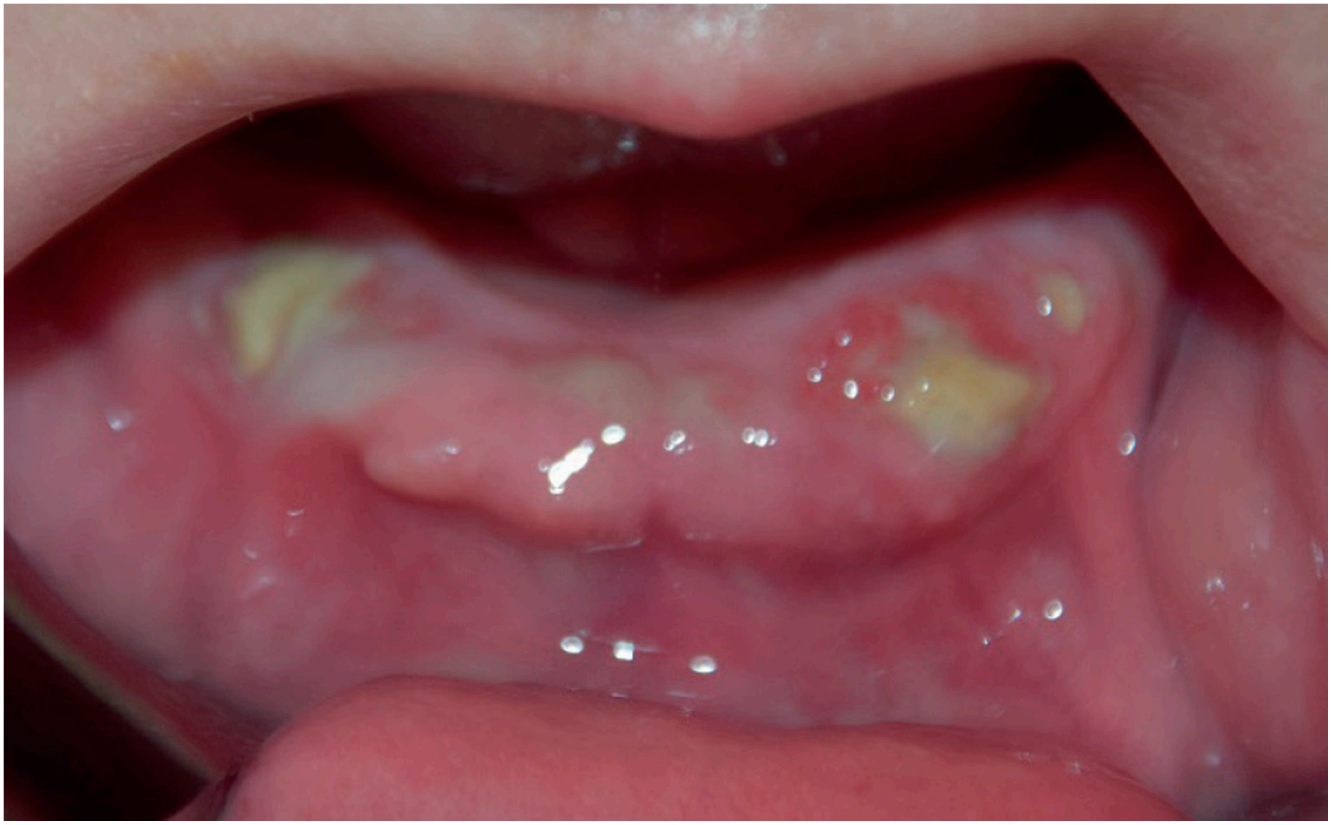

Figure 1. Intraoral image. The exposed bone of the alveolar part of the mandible.

2.3. Timeline

The main events concerning the course of the described MRONJ case are presented graphically in Table 1.

Table 1. Case timeline.

February 2018	Termination of Docetaxel Administration
↓	
March 2018–August 2018	Administration of zoledronate
↓	
October 2018	Tooth extraction
↓	
February 2019–March 2019	MRONJ diagnostic and treatment
↓	
March 2019	The beginning of prosthetic rehabilitation

2.4. Diagnostic Assessment

An orthopantomogram was taken as a basic imaging examination. In the next stage, a computed tomography both with and without contrast, covering the craniofacial area, was ordered. This examination revealed an area of sclerosis with a periosteal reaction in

the mandibular body. The alveolar part of the mandible revealed a rupture of the cortical layer, as well as a radiographic image of the osteolytic process. The extent of osteolysis on the labial side exceeded the alveolar part of the mandible, and reached the base of this bone. Moreover, numerous osteosclerotic focal lesions, corresponding to metastases, were found in the imaged part of the cervical spine, as well as in the bones of the skull. Imaging tests alone did not allow for a diagnosis of the pathology of the mandible. The radiologist describing the examination emphasized the need to differentiate inflammatory lesions from neoplastic ones, i.e., prostate cancer metastases. Computed tomography images, both without and with contrast, respectively, are presented in Figures 2 and 3. A biopsy of the bone tissue and gingiva showed no signs of neoplasm. Taking into account all of the above data, the initial diagnosis of MRONJ at Stage 3 was made according to the AAOMS classification from 2014 [21].

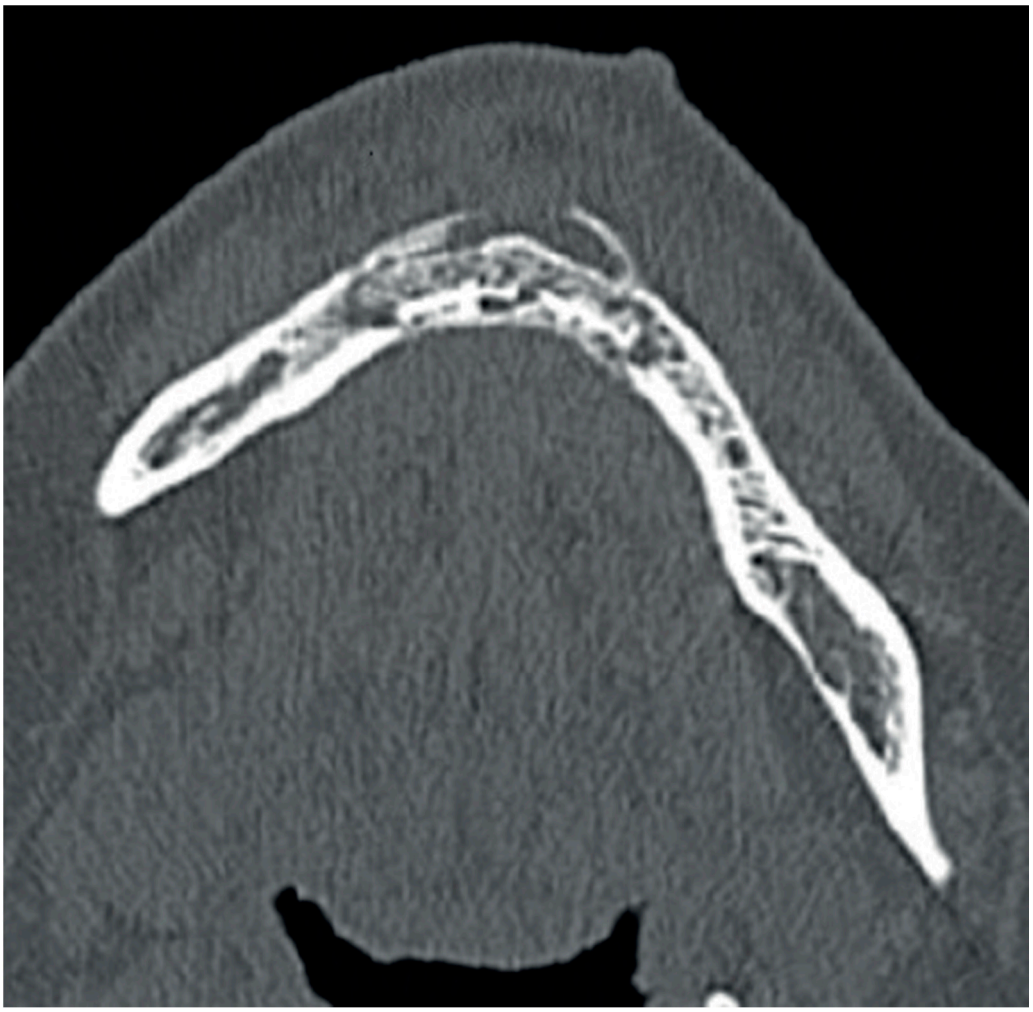

Figure 2. Computed tomography without contrast. Osteonecrosis of the mental section of the mandibular body.

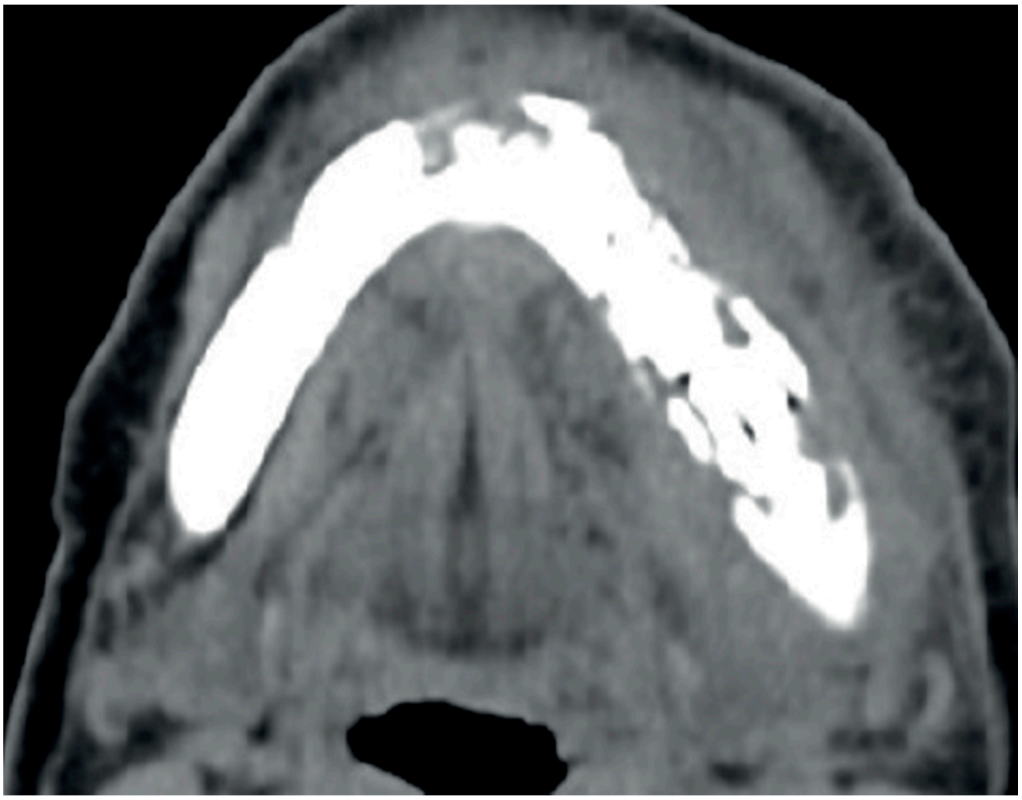

Figure 3. Computed tomography with contrast. Multifocal necrotic changes of the mandibular body in the mental sections and the left molar area.

2.5. Therapeutic Intervention

As the main therapeutic surgery stage, a marginal resection of the mandibular body was performed. First, the gingiva and the periosteum were cut through the gingival defects at the top of the alveolar part of the mandible. Vertical release incisions were made bilaterally in both molar regions. Then, the mucoperiosteal flap was detached in the mouth vestibule, and a swab from the bottom of the wound was taken for bacteriological examination. Further elevation of the flap exposed mental foramen in the mandible. The vestibular flap was mobilized by preparation around the intact mental nerves. In the next stage, the mucoperiosteal flap was detached from the lingual side. No release cuts were made on the lingual side, thereby maintaining the envelope character of the flap. Using a piezoelectric saw, a block of macroscopically altered bone was cut out, along with a margin of macroscopically unchanged bone. The entire bone block containing the necrotic part was submitted for histopathological examination. The linguo-inferior continuity of the mandibular bone was preserved. Then, the bone edges were smoothed, obtaining an image of a healthy, properly blood-supplied bone along the entire section. The edges of the lingual and vestibular flaps were surgically prepared, and sutured tightly without difficulty. The image of the mandibular bone after the detachment of the labial mucoperiosteal flap is shown in Figure 4.

In addition to the current pharmacotherapy, the patient received drugs supporting the process of surgical treatment of MRONJ. From the day of admission to hospital, the patient received 1.5 g of cefuroxime every 8 h. In accordance with the procedures adopted in our clinic, in the absence of contraindications, cefuroxime is administered prophylactically, and as empirical antibiotic therapy. In the described case, the antibiogram confirmed the need to continue using cefuroxime as a targeted antibiotic therapy. The following microorganisms were found to be present in the wound: numerous *Escherichia coli*, and small numbers of *Enterococcus faecalis*, *Streptococcus anginosus*, *Streptococcus mitis*. During hospitalization, cefuroxime was administered intravenously. After discharge, oral adminis-

tration was continued at a dose of 500 mg every 12 h for 5 days. Taking into account the thromboembolic mechanism of MRONJ development, the patient was also administered 0.6 mg of enoxaparin daily throughout the hospitalization period (9 days). Analgesic pharmacotherapy was applied from the day of admission to hospital, and was modified depending on the symptoms, with a particular emphasis on the perioperative period. This was 1 g of paracetamol every 8 h and 50 mg of ketoprofen on demand in case of pain (no more than 100 mg every 8 h). The type and dosage of analgesics did not differ from the standards of maxillofacial surgery. In the perioperative period, i.e., from admission to hospital until resection, and for the 2 weeks following surgery, the patient was ordered to rinse the mouth with a 0.12% chlorhexidine solution.

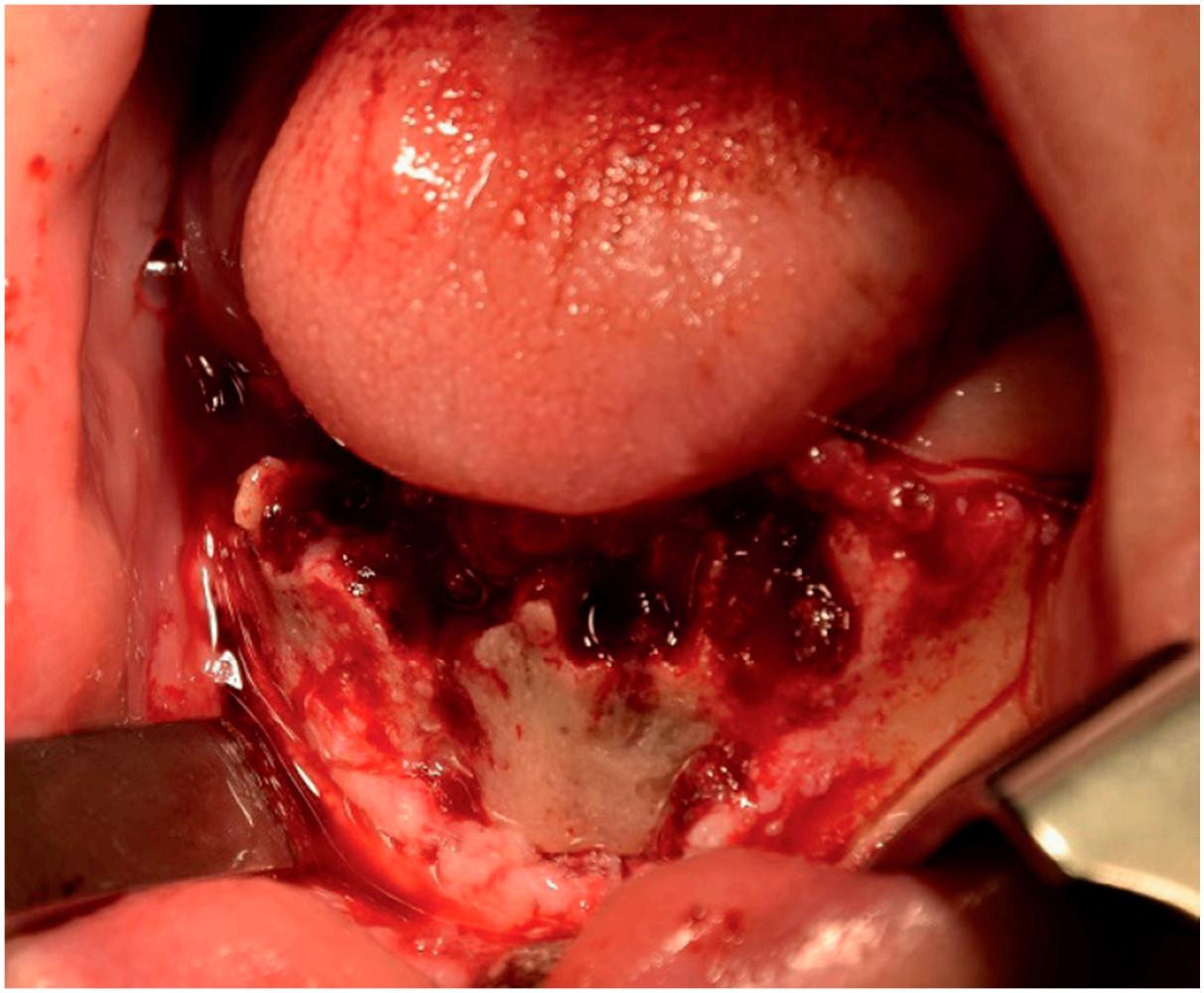

Figure 4. Intraoperative view. Osteonecrosis of the mandible in the anterior region.

3. Results

The patient was discharged from hospital on 4 March 2019, and referred for outpatient care. Healing of the wound proceeded without complications, and the removal of the sutures completed the surgical treatment stage. A control panoramic radiograph taken approximately 10 weeks after surgery showed normal bone healing (Figure 5). The histopathological examination revealed non-specific granulation tissue and necrotic bone in the state of purulent inflammation. No tumor features were found in the material tested. Therefore, the diagnosis of MRONJ at Stage 3 according to the AAOMS classification from 2014 was confirmed [21]. Due to the patient's general condition, i.e., advanced neoplastic disease, it was not decided to surgically reconstruct the defect of the alveolar part and the mandibular body after marginal resection. Possible methods of microsurgical, distractive,

or augmentative defect reconstruction were considered inappropriate in this situation. Instead, the patient was referred for prosthetic rehabilitation, which was well received, due to many years of experience in wearing upper dental prosthesis. A set of removable dentures was produced. Subsequent visits did not take place due to the deterioration of patient's health. The patient died in June 2020 of a myocardial infarction.

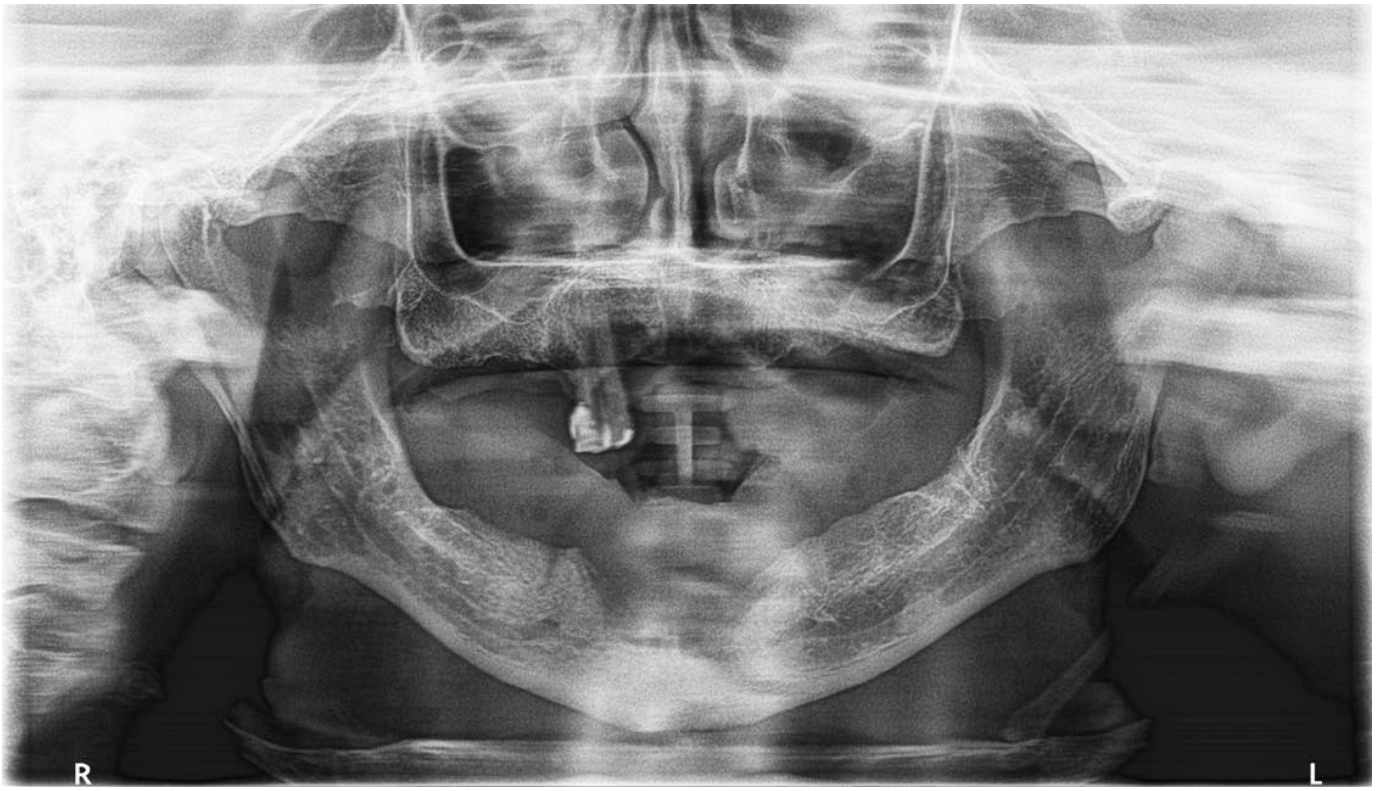

Figure 5. Postoperative control panoramic radiograph.

4. Discussion

The real incidence of MRONJ is difficult to assess [1,7,8,12,19]. Considering the low clinical significance and diagnostic difficulties, it can be assumed that reliable reporting of cases from AAOMS stages 0 and 1 is questionable [11,21]. Studies aimed at calculating the incidence of MRONJ give different results [1,7,8,12,19]. Limones et al. determined that the risk of developing MRONJ from taking zoledronic acid alone for 3 years is between 1% and 2.3% [12]. Hallmer et al. report the incidence rate of MRONJ due to intravenous bisphosphonate intake to be around 1% [7]. Galis et al. report less than 4% of the risk of MRONJ as a result of antiresorptive therapies in prostate cancer [1]. Ueda et al. report that MRONJ occurs in as many as 17.7% of patients treated with bone-modifying agents in the diagnosis of cancers [19].

The factors initiating the development of MRONJ may be alveolar surgery and injuries, mainly due to the wearing of dentures [6,25]. This is why new materials for the production of prostheses are being developed, which, at the same time, meet the requirements of strength and high biocompatibility to ensure easy healing of minor sores arising during the adaptation phase [25–27]. In the reported case, the most likely factor that initiated the development of necrosis were multiple extractions of the mandibular teeth. The patient probably never used the lower prosthesis. It is possible that the performed extractions were to be a preparation for prosthetic treatment.

The diagnosis of MRONJ requires the identification of bone which is exposed or accessible by probing [21,28]. The AAOMS classification of 2014 is commonly used to assess the severity of MRONJ [21,28,29]. The latest attempt to implement the new classification

known to the authors of this study belongs to Yoneda et al. [29]. Nevertheless, published in 2019, guidelines for the prevention, diagnosis, and treatment of MRONJ developed by the United Kingdom Chemotherapy Board are based on the AAOMS classification [28]. The case we described was classified as AAOMS Stage 3 due to the necrotic lesions of the mandibular base.

The 2014 AAOMS guidelines for MRONJ Stage 3 treatment indicate: (1) the need for antiseptic mouthwash; (2) antibiotic therapy; (3) analgesic drug therapy; and (4) surgical debridement or resection [21]. The standard antiseptic mouthwash used is 0.12% chlorhexidine solution, prescribed as a prescription drug or a ready-made preparation [30,31]. Pardo-Zamora et al. and Heifetz-Li et al. propose the use of such a rinse every 12 h for up to 30 days, referring to the recommendations of other authors [30,31]. The preferred antibiotics in the prophylaxis and treatment of MRONJ are those from the penicillin group (e.g., amoxicillin) and clindamycin [32–34].

The basis for planning a surgical procedure in the course of MRONJ therapy is proper imaging diagnostics [35–37]. The imaging tests that allow for the initial diagnosis and rough estimation of the extent of necrosis are small-image X-rays and orthopantomogram images [36]. In the next stage, computed tomography is ordered to determine the scope of the necessary resection in three dimensions [36,37]. Some authors note the usefulness of single photon emission computed tomography (SPECT), inter alia, in predicting the expected extent of recurrence in the most advanced cases [35]. Accurate assessment of the correct extent of tissue excision, particularly within healthy margins, is a current challenge [36,38]. Recent studies also indicate the usefulness of the fluorescence phenomenon used in the form of fluorescence-guided surgery (FGS) [38,39].

The surgical procedure itself, depending on the previously established scope, takes the form of curettage of necrotic masses, marginal resection of the mandible, or segmental resection of the mandible [22]. In addition, this extent of surgical excision implies further treatment [22,40]. Small cavities are left to heal spontaneously, while the larger ones may require bone surface modeling, as implemented in our case, or additional reconstructive procedures [22,40]. Among them, bone augmentations as non-vascularized or vascularized grafts are possible [40,41]. The latter are a typical reconstructive solution in cases of breaking the continuity of the mandible due to resection [41].

An important element of local treatment is the adequate protection of the wound, i.e., healthy bone exposed during the procedure and, possibly, transplanted bone [40,42,43]. Numerous reports indicate the possible benefits of using platelet-rich fibrin (PRF) dressings [30,42,44]. The technique is so readily available and promising that it may become a standard in the treatment of MRONJ in the future [30,42,44]. At the same time, the key role of tightening the wound, and thus covering the exposed, vulnerable bone with adjacent flaps, must not be forgotten [43]. Marcianò et al. distinguish here simple muco–periosteal flaps, advanced and rotated flaps, and plasty with local flaps [43]. This division provides a clear ladder of soft tissue management capabilities in MRONJ cases [43].

5. Conclusions

The cases of bisphosphonate-induced MROJ, known since 2004, are a current problem. MRONJ therapeutic methods, although known, are undergoing development, which forces us to constantly update our knowledge about them. MRONJ can develop covertly, with scanty clinical symptoms, and can be easily overlooked. Radical combined treatment may, in some cases, prevent the further progression of the disease, which was successful this time.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: All published data on the described case are available in the main body of this article.

Conflicts of Interest: The authors declare no conflict of interest.

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