oral

MDPI

Case Report

Clinical and Histological Evaluation of Jaw Osteonecrosis Unrelated to Anti-Bone Resorption Drugs

Cinzia Casu [1,*], Andrea Butera [2,*], Andrea Scribante [2,3] and Germano Orrù [1]

[1] Oral Biotechonology Laboratory, Department of Surgical Science, University of Cagliari, 09121 Cagliari, Italy; orru@unica.it
[2] Unit of Dental Hygiene, Section of Dentistry, Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, 27100 Pavia, Italy; andrea.scribante@unipv.it
[3] Unit of Orthodontics and Paediatric Dentistry, Section of Dentistry, Department of Clinical, Surgical, Diagnostic and Paediatric Sciences, University of Pavia, 27100 Pavia, Italy
* Correspondence: cinzia.casu2@unica.it (C.C.); andrea.butera@unipv.it (A.B.)

Abstract: Medication-related osteonecrosis of the jaw (MRONJ) is a multifactorial condition defined as an adverse drug reaction that results in progressive jawbone destruction and necrosis in individuals treated with certain medications, occurring without a history of prior radiotherapy. These drugs are mainly bisphosphonates, denosumab, and other bone-modifying agents, anti-angiogenic agents such as anti-endothelial growth factor, tyrosine kinase inhibitors, and proteins classified as mammalian targets of rapamycin. The diagnosis of MRONJ is based on clinical (exposed jawbone, fistula with pus, hyperplasia of the mucosa overlying the necrotic bone tissue) and radiological evaluation. We report four cases of clinical and radiological evidence of osteonecrosis of the jaw that are unrelated to the use of antiresorptive or anti-angiogenic agents. In two instances, histological and microbiological evidence was also found (high concentration of Actinomyces, the microbe most commonly found in oral sites affected by MRONJ). These atypical cases are reported to highlight the possibility that other, previously undocumented, drugs may also contribute to the development of ONJ

Keywords: osteonecrosis of the jaw; MRONJ; Actinomyces; oral microbiological evaluations; atypical ONJ

check for updates

Academic Editor: Ourania Nicolatou-Galitis

Received: 13 November 2024
Revised: 20 January 2025
Accepted: 27 March 2025
Published: 24 April 2025

Citation: Casu, C.; Butera, A.; Scribante, A.; Orrù, G. Clinical and Histological Evaluation of Jaw Osteonecrosis Unrelated to Anti-Bone Resorption Drugs. *Oral* **2025**, *5*, 29. https://doi.org/10.3390/oral5020029

Copyright: © 2025 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a multifactorial disease in which there is necrosis with jawbone exposure; the same often appears as if not covered by gum tissue, and is associated with the use of bisphosphonates, denosumab, and anti-resorptive agents [1]. Alterations of the blood microcirculation, bone metabolism, masticatory and non-masticatory trauma to which the maxillary and mandibular bone is subjected, and exposure of the oral cavity to a high microbial concentration have been considered among the most important factors in the development of MRONJ [2,3]. Dental extractions, implant procedures, oral and maxillofacial surgeries, periodontal disease, and invasive periodontal procedures have been identified as risk factors for the development of MRONJ. Infection/inflammation, immune system dysfunction, angiogenesis inhibition, soft tissue toxicity, and systemic disorders related to conditions such as rheumatoid arthritis or diabetes mellitus are other predisposing factors in patients subjected to these types of drugs and not to radiation therapy of the head and neck [1,4]. Diagnosis is based on clinical findings supported by radiological signs [1].

The use of instrumental radiographic investigations, in particular three-dimensional ones, is necessary to establish the expansion at the bone level of the osteonecrosis process, the involvement of noble structures (mandibular canal, maxillary sinus), and staging evaluation [1,5].

At a radiological level, a radiolucency can often be observed, corresponding to the osteonecrotic area, which is more identifiable with three-dimensional images [6].

There is a staging of MRONJ based on the extension of the osteonecrotic process, which divides it into stages 0, 1, 2, and 3, the latter being with cutaneous fistula. However, there are conflicting opinions in the international scientific literature regarding the staging of MRONJ. In the AAOMS (American Association of Oral and Maxillofacial Surgeons) classification, in fact, a radiological staging of MRONJ is not considered, but is mainly linked to the clinical presentation, to avoid overestimating the prevalence of the disease itself, declaring "may overestimate the true disease frequency by including false positives in the numerator." The SIPMO–SICMF (Società Italiana di Medicina e Patologia Orale–Società Italiana di Chirurgia Maxillo-Facciale) staging instead involves a stage 1 defined as "focal MRONJ" in which there are radiological signs of thinning or erosion of the cortex and light osteolysis of the marrow; a stage 2 defined as "Diffuse MRONJ" in which at a radiological level there is, essentially, widespread ostelolysis of the bone marrow and possible presence of sequestration; and a stage 3 defined as "Complicated MRONJ" with radiological signs of osteosclerosis of adjacent bones (zygoma and hard palate), pathological fracture, osteolysis extending to the maxillary sinus and/or sinus tract (oroantral, oronasal fistula, orocutaneous). Each stage could be subdivided into *a* or *b*, taking into account the patient's symptom(s) [5].

The treatment is based on prolonged antibiotic therapy, the adjuvant use of topical antiseptics, and is sometimes inevitably associated with surgery, such as debridement and bone resection in cases refractory to medical therapy (stage II and III) [1,7].

The drugs linked to the development of MRONJ, in a very recent paper published in 2024, are bone-modifying agents (BMAs): bisphosphonates (BPs) and denosumab (DMB); antiangiogenic agents (AAs): anti-endothelial growth factors (VEGFs, e.g., bevacizumab), tyrosine kinase inhibitors (TKIs, e.g., sunitinib), and proteins classified as mammalian targets of rapamycin (mTORs, e.g., everolimus) [5].

The aim of this work is to report four atypical clinical cases of osteonecrosis of the jaw bones that are unrelated to anti-bone resorption drugs or other drugs reported in the previous recent literature.

The clinical and radiological characteristics in all four cases presented in this work are comparable to MRONJ but none of the four patients have ever taken bisphosphonates, monoclonal antibodies, or other anti-bone resorption or antiangiogenetic drugs. These patients are two women and two men, three of whom underwent surgical maneuvers of the oral cavity on the jaw before developing bone lesions indicative of MRONJ, which recurred after several weeks, with radiographic signs of bone resorption.

2. Case Series

Case 1. In March 2021, a 48-year-old female patient who had undergone extraction of element 48 was placed under our observation due to an asymptomatic lesion on the mylohyoid line, which was located very close to the site of the extraction that took place a few months earlier (Figure 1a). Orthopantomography X-ray and CT evaluation showed a great resorption of the bone at the site involved (Figure 1b,c). The patient denied current or previous anti-resorptive drug use and to have been treated with radiotherapy. She regularly took an anti-hypertensive drug (olmesartan) and was normotensive. She had previously undergone antibiotic therapy with amoxicillin + clavulanic acid (1000 mg)

for prolonged periods, and a debridement of the exposed bone region with a very small improvement (Figure 1d). The patient was sent to the hospital for excision of the area and histological evaluation. We do not have feedback from the patient at this time. The type of the exposure and the radiological signs in the CT could be related to STAGE 2a, following the SIPMO-SICMF criteria for MRONJ staging [5].

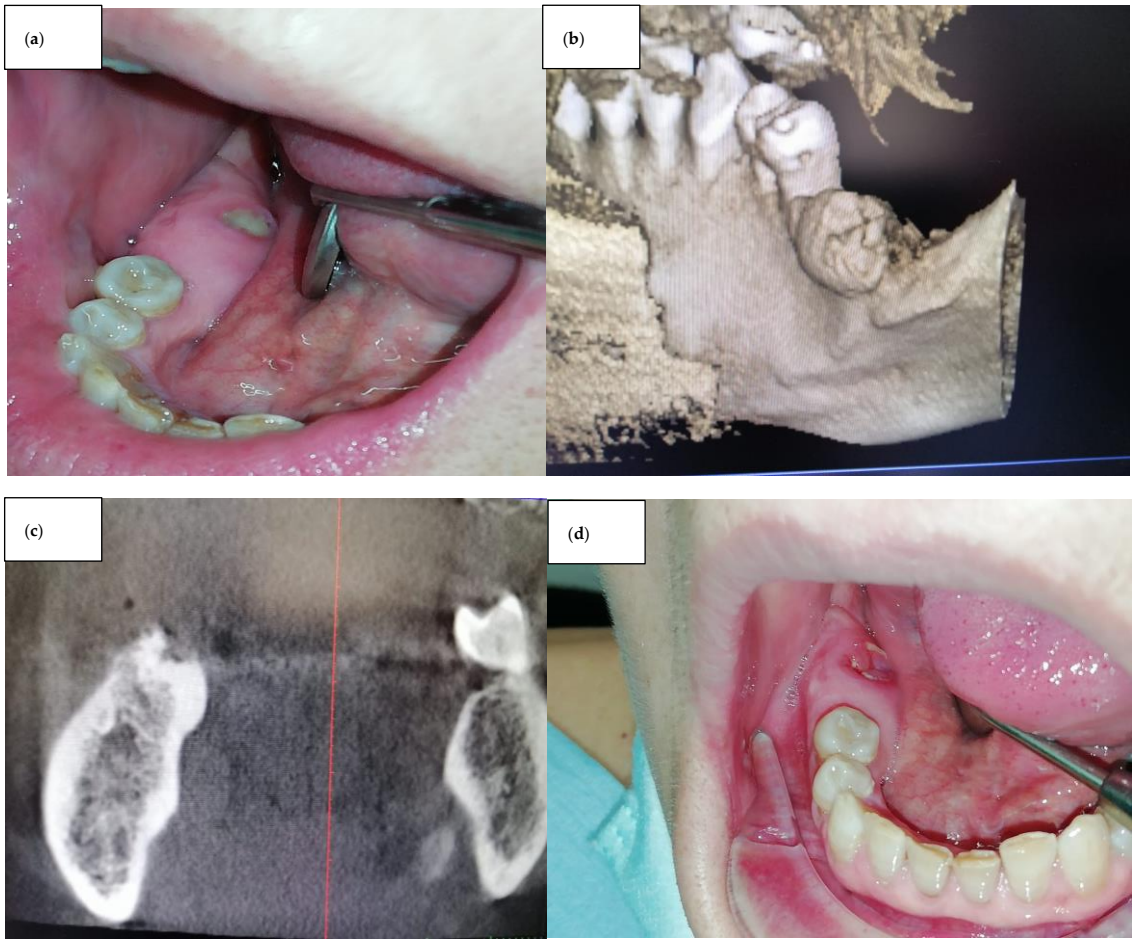


Figure 1. (**a**) Bone exposure at the mylohyoid line several months after surgical extraction. (**b**) Bone resorption presentation on the lingual side of the mandible. (**c**) CT section of the jawbone lesion. (**d**) Exposed bone on the mylohyoid line with small improvement after prolonged poli-antibiotic therapy.

Case 2. In November 2022, a female patient presented to our observation for the evaluation of an asymptomatic fistula in site 48–47 on the lingual side that was recurrent and had developed since August 2022, following extraction of element 48 (Figure 2a). The patient's medical history reported only a pollen allergy and they denied current or previous use of anti-resorptive or antiangiogenetic drugs or radiotherapy. On oral x-ray (Figure 2b) she showed signs of bone resorption, while on a CT radiographic examination it was not possible to intercept important radiological signs. This lesion could be classified as STAGE 1a following the SIMPO–SICMF criteria for MRONJ staging. Following prolonged antibiotic therapy with amoxicillin + clavulanic acid (1000 mg) in December 2022, the lesion had resolved completely.

Case 3. In June 2023, a 74-year-old male patient came for a check-up. In 2021, the patient received a diagnosis of oral squamous cell carcinoma in situ on a pre-existing leukoplakia in the lower left alveolar–gingival mucosa, which was treated with a simple wide surgical excision without radiotherapy. The patient also had well-compensated type 2 diabetes and took an anti-hypertensive drug (olmesartan) and an anti-platelet aggregator

(ticlopidine). Following recurrence of leukoplakia on the lingual–gingival side around the area of 37–38 and in the gingival area distal to 27, he underwent an excisional biopsy of both lesions, measuring 5 and 3 mm, respectively.

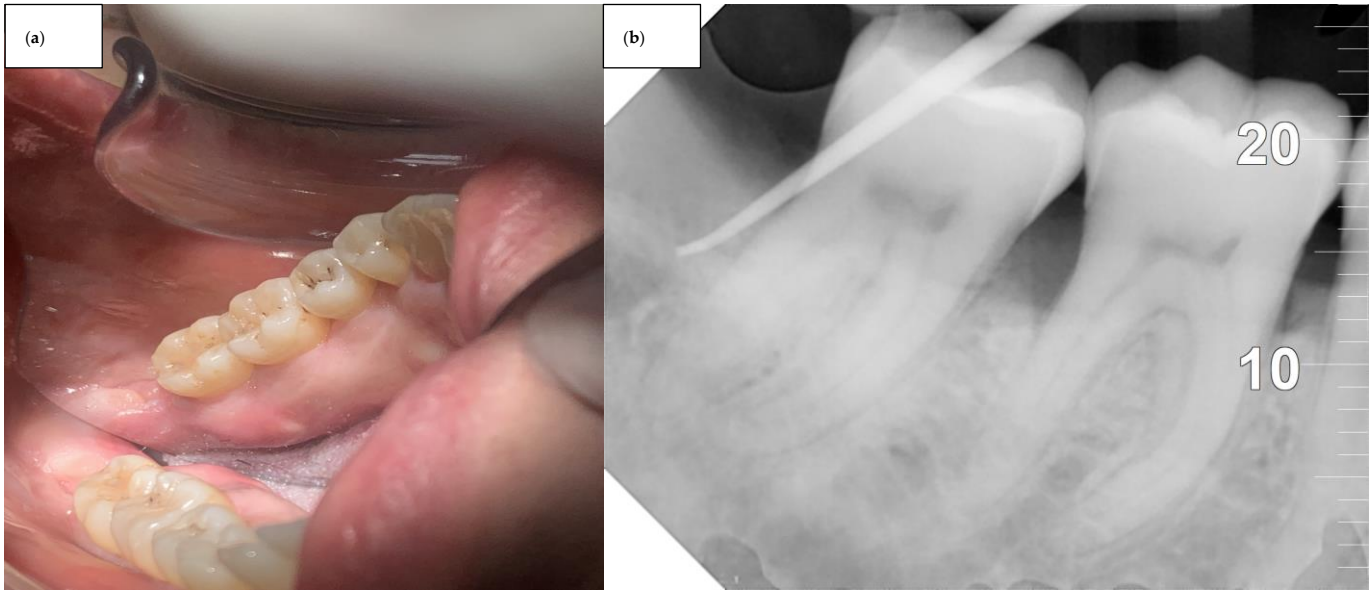


Figure 2. (**a**) Fistula on mylohyoid line several weeks after 3.8 extraction and refractory to antibiotic therapy. (**b**) Oral x-ray with a guttapercha point showing the origin of the lesion.

From the following days until the day of the check-up (about 1 month and a half), the patient noticed some discomfort in the area and the absence of healing of the wound. In correspondence with the areas, it was possible to see two bony exposures, painful on palpation, with a small bone sequestration on the mandibular lesion (Figure 3a). The small sequestrum was removed, placed in 4% paraformaldehyde, and sent for histological evaluation (Figure 3b). A further biological sample was taken from the lesion by using a sterile transport swab (FL medical, Torreglia, Italy). This sample was smeared on a microscope slide, air-dried and heat-fixed for 20 s. A Gram-stain test was then performed for the microscopic evaluation.

The patient had been subjected to amoxicillin + clavulanic acid (1000 mg) + metronidazole (250 mg), three times a day for 20 days, as required by the protocol for the treatment of stage 1 MRONJ. The patient immediately noticed important improvements and after 3 weeks complete healing of the lesion occurred. A new CT was been prescribed, which showed no radiological signs of bone lesions. The histological examination of the bone fragment highlighted bone tissue affected by osteonecrosis. The sample taken from the MRONJ lesion and stained using the Gram method, as explained above, had typical structures for Actinomyces (multiform filaments that are positive for gram), which are typical cells of sites affected by MRONJ. Our findings are close to the results found by Ibrahim et al. [8] (Figure 3c–e). This lesion could be classified as STAGE 1b following the SIMPO–SICMF criteria for MRONJ staging.

Case 4. In December 2023, a 75-year-old male patient came to my attention due to the presence of a mandibular lesion in the 36–37 region on the lingual side, in the absence of the molar elements. The patient had a previous diagnosis of adenocarcinoma on the hard palate in 2006 and underwent several radiotherapy sessions for the following months. The patient and his family doctor denied current or past use of anti-bone resorption drugs. The patient underwent carotid stent surgery in 2018 and suffered from a gastric ulcer in 2019. He currently takes an anti-platelet drug, clopidogrel, nebivolol, and olmesartan to control

arterial hypertension. At a clinical level it was possible to observe the presence of a fistulous tract, painful on palpation, with intense edema around it that was very rough on palpation. The patient also showed a cutaneous fistula with purulent exudate corresponding to the intra-oral lesion.

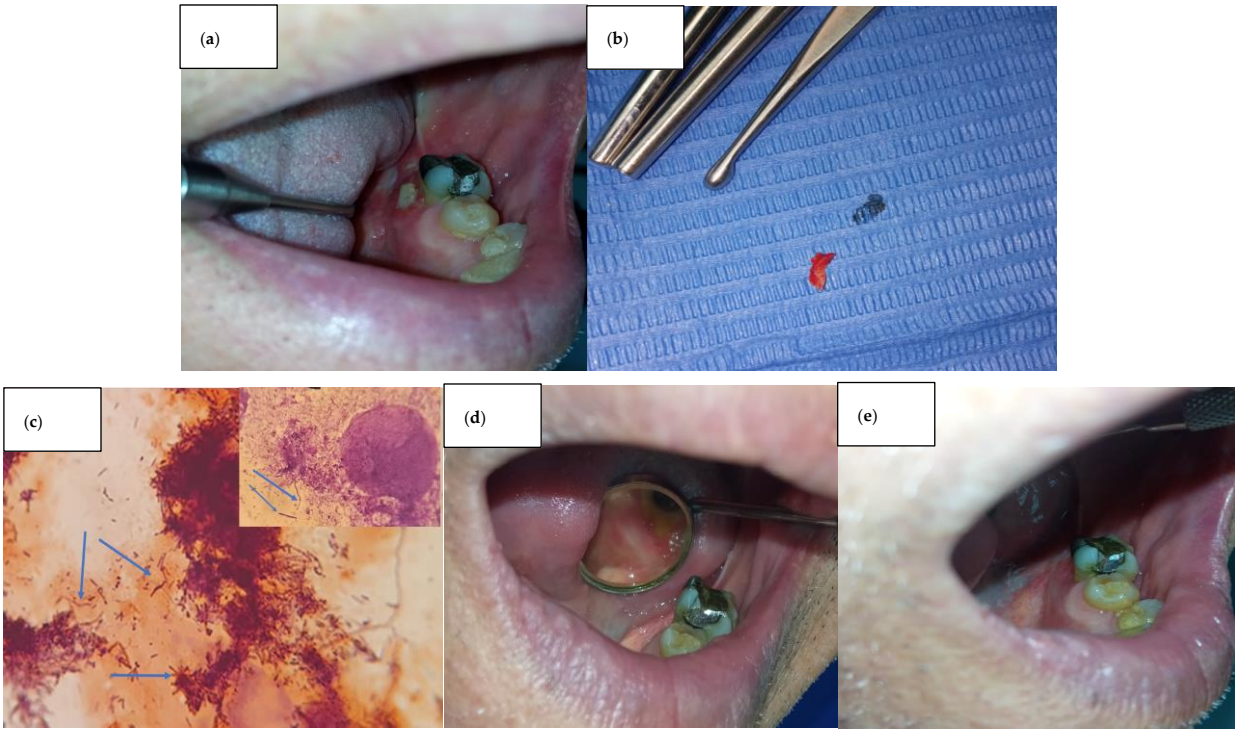


Figure 3. (**a**) Bone exposure in the mylohyoid line after surgical removal of gingival leukoplakia. (**b**) Bone sequestrum sent for histological evaluation. (**c**) Sample observed under optical microscope. It showed filament-like structures (arrow) radiating from the biofilm core (Gram stain, image taken at 1000× magnification). (**d**) Bone lesion healing after poli-antibiotic therapy for MRONJ, indirect vision. (**e**) Bone lesion healing after poli-antibiotic therapy for MRONJ, direct vision.

Through the CT examination, it was possible to observe a large osteolytic area with slight interruption of the cortex in the site corresponding clinically to the fistula (Figure 4a). The patient had already undergone previous therapies with a single antibiotic and SRP (scaling and root planning) of the molar region without success. Then he was subjected to therapy with amoxicillin + clavulanic acid (1000 mg) and metronidazole (250 mg), three times a day for a total of 25 days, in addition to rinses with 1% hydrogen peroxide, during which the lesion significantly reduced in size, no longer produced purulent exudate, and a bony sequestrum was expelled spontaneously, which was then subjected to histological examination (Figure 4b,c). The report confirmed the diagnosis of necrotic tissue related to ONJ. This lesion, for the clinical and radiological features, could be classified as STAGE 3b, following the SIMPO–SICMF criteria for MRONJ staging. The patient has been subjected to Low Level Laser Therapy (6 sessions) with an 810 nm diode laser, 0.5 watt of power, performed one month later. The patient was healed after 2 months from the first visit (Figure 4d,e).

A new CT was performed after clinical healing to confirm the absence of radiological signs.



Figure 4. (**a**) CT evaluation of the osteolysis. (**b**) Bone sequestrum with teeth of the area of the mylohyoid line sent for histological evaluation. (**c**) Patient immediately after the spontaneous removal of the bone sequestrum with teeth. (**d**) Healing after poli-antibiotic therapy for MRONJ, bone debridement, and six sessions of LLLT; lingual view. (**e**) Healing after poli-antibiotic therapy for MRONJ, bone debridement, and six sessions of LLLT; vestibular view.

3. Discussion

As previously mentioned, in the most recent scientific literature, a patient is defined as suffering from MRONJ if he has taken or is taking certain types of drugs. [5]. These drugs belong to bone-modifying agents, such as bisphosphonates and denosumab (DMB), antiangiogenic agents, TKIs, and mTORs [5]. In the clinical cases described, in no case had these types of drugs been taken by the patients; therefore, at first glance, one might think that these patients do not suffer from osteonecrosis.

Scientific evidence that other drugs, in addition to those already mentioned, may also be responsible or co-responsible for MRONJ is present in the literature, including one case linked to Tolicizumab taken to treat COVID-19 [9,10].

According to the most recent reviews of the literature, bone exposure is no longer considered the only clinical form of presentation of MRONJ; in fact, more and more cases are observed with the presence of a fistula with leakage of exudate without exposure of necrotic bone, as we can observe in case 2, in addition to also having forms with hyperplasia of the mucosa overlying the necrotic bone tissue [5].

Although the diagnosis of MRONJ is essentially based on the clinical, radiological investigations are considered important in the diagnostic process and for the clinical staging. However, some researchers have recently demonstrated that many cases of MRONJ did not have signs of bone resorption (marked radiolucency, without osteolysis) when observed with computed tomography (CT), as we observed in presented cases 2 and 3. Furthermore, in these cases, it seems that recovery is faster and that these cases respond better to drug

therapy [11], as we saw in cases 2 and 3 compared to cases 1 and 4. In the patients described, radiographic follow-up was not possible in case 1, because the patient did not return for their follow-up appointment. In case 2, a new evaluation with CT was not carried out after complete closure of the fistula because at the first observation the signs of radiological involvement were not evident, while in cases 3 and 4, control CTs were performed and confirmed the absence of lesions.

Among the microbial population present within the necrotic tissue taken from patients affected by MRONJ, the most found microbes are Actinomyces, which are present in approximately 82% of MRONJ cases [8,12]. In case 3, we intercepted a large concentration of Actinomyces, thanks to a simple brush sampling, which was non-invasive for the patient, that was used for cell culture in a special medium.

All four patients had the mandible lesion on the typical site of MRONJ, clinical and radiological aspects of MRONJ, and two of them had a histological confirmation [1–3]. In three out of the four cases presented, the patients were undergoing treatment with anti-hypertensive drugs (olmesartan), and in cases 3 and 4 we can also note the association with an anti-platelet drugs (ticlopidine, clopidogrel). In the scientific literature, we have not found any previous cases of MRONJ related to anti-hypertensive and/or anti-platelet drugs. [5,10,13].

The use of some types of anti-platelet agents has even been proposed in the prevention and management of ONJ, but so far never related to its onset [14].

These four cases could shed light on a new oral pathological entity or on the possibility that additional drugs, compared to those already documented, can cause ONJ; these are drugs taken very frequently by patients with which all medical specialties must be able to accommodate. The exact etiology of MRONJ remains unknown to this day, even though over 20 years have passed since this multifactorial disease was first identified (2003). At the beginning it was defined as BRONJ because it was only observed in patients taking bisphosphonates; in 2016, when the correlation with other drugs was also discovered, its name was changed to MRONJ.

During this time frame, definitions and clinical manifestations have changed, and new etiological factors have been identified. All of these advances started from the reporting of atypical cases.

Future investigations are needed in order to explore new treatment strategies, including antioxidant administration [15–18], ozone application [19–22], and photobiomodulation [23–26]. These recently introduced compounds and techniques showed promising results in dentistry and periodontology and could also be considered, as adjuvants, for ONJ integrated therapy.

4. Conclusions

In the four cases described with a diagnosis of ONJ, none of the patients were taking anti-bone resorption or anti-neoangiogenic drugs, such as those described in the latest position paper published in 2024; however, three out of four patients were taking anti-hypertensive drugs. This suggests that there are other drugs that could potentially cause MRONJ and that it is necessary to report cases not related to the intake of anti-bone resorption or anti-neoangiogenic drugs, like these, to prevent the risk of ONJ in other patients.

Author Contributions: Conceptualization, C.C. and G.O.; methodology, C.C.; software, A.S.; validation, A.B., A.S. and G.O.; formal analysis, A.S.; investigation, C.C.; resources, A.B.; data curation, A.B.; writing—original draft preparation, A.B.; writing—review and editing, C.C.; visualization, A.S.; supervision, G.O.; project administration, C.C.; and funding acquisition, G.O. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. Per local standards, our universities do not require ethical approval or institutional review board approval for reporting individual cases or case series when informed consent is provided by the patient.

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

Data Availability Statement: Data are available upon reasonable request at the Corresponding Authors.

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

References

1. Laputková, G.; Talian, I.; Schwartzová, V. Medication-Related Osteonecrosis of the Jaw: A Systematic Review and a Bioinformatic Analysis. *Int. J. Mol. Sci.* **2023**, *24*, 16745. [CrossRef] [PubMed] [PubMed Central]
2. Jiang, A.; Zhang, Z.; Qiu, X.; Guo, Q. Medication-related osteonecrosis of the jaw (MRONJ): A review of pathogenesis hypothesis and therapy strategies. *Arch. Toxicol.* **2024**, *98*, 689–708. [CrossRef] [PubMed]
3. Byrne, H.; O'Reilly, S.; Weadick, C.S.; Brady, P.; Ríordáin, R.N. How we manage medication-related osteonecrosis of the jaw. *Eur. J. Med. Res.* **2024**, *29*, 402. [CrossRef] [PubMed] [PubMed Central]
4. Dipalma, G.; Inchingolo, A.D.; Piras, F.; Palmieri, G.; Pede, C.D.; Ciocia, A.M.; Siciliani, R.A.; Olio, F.D.; Inchingolo, A.M.; Palermo, A.; et al. Efficacy of guided autofluorescence laser therapy in MRONJ: A systematic review. *Eur. Rev. Med. Pharmacol. Sci.* **2023**, *27*, 11817–11831. [CrossRef] [PubMed]
5. Bedogni, A.; Mauceri, R.; Fusco, V.; Bertoldo, F.; Bettini, G.; Di Fede, O.; Lo Casto, A.; Marchetti, C.; Panzarella, V.; Saia, G.; et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). *Oral Dis.* **2024**, *30*, 3679–3709. [CrossRef] [PubMed]
6. Nisi, M.; Gennai, S.; Graziani, F.; Barone, A.; Izzetti, R. Clinical and radiologic treatment outcomes of implant presence tirggered-MRONJ: Systematic review of literature. *Oral. Dis.* **2024**, *30*, 5255–5267. [CrossRef] [PubMed]
7. Sharma, S.; Shankar, R.; Ravi Kiran, B.S.; Breh, R.; Sarangi, S.; Kumar Upadhyay, A. A Narrative Review of Osteonecrosis of the Jaw: What a Clinician Should Know. *Cureus* **2023**, *15*, e51183. [CrossRef] [PubMed] [PubMed Central]
8. Ibrahim, N.; Apandi, N.I.M.; Shuhardi, S.A.; Ramli, R. *Actinomyces* sp. Presence in the Bone Specimens of Patients with Osteonecrosis of the Jaw: The Histopathological Analysis and Clinical Implication. *Antibiotics* **2022**, *11*, 1067. [CrossRef] [PubMed] [PubMed Central]
9. Konarski, W.; Poboży, T.; Konarska, K.; Śliwczyński, A.; Kotela, I.; Krakowiak, J. Exploring the Impact of Novel Anti-Cancer Therapies on Jaw Osteonecrosis and Other Bones: A Comprehensive Review. *J. Clin. Med.* **2024**, *13*, 1889. [CrossRef] [PubMed] [PubMed Central]
10. Roh, T.; Jo, H.; Kim, J.Y. Maxillary Bone Necrosis in Post-COVID-19 Patients: Possibility of Medication-Related Osteonecrosis of Jaws (MRONJ) Induced by Tocilizumab. *J. Craniofac. Surg.* **2024**, *35*, e454–e457. [CrossRef] [PubMed]
11. Kojima, Y.; Sawada, S.; Sakamoto, Y. Medication-related osteonecrosis of the lower jaw without osteolysis on computed tomography images. *J. Bone Miner. Metab.* **2024**, *42*, 27–36. [CrossRef] [PubMed]
12. Cerrato, A.; Zanette, G.; Boccuto, M.; Angelini, A.; Valente, M.; Bacci, C. Actinomyces and MRONJ: A retrospective study and a literature review. *J. Stomatol. Oral Maxillofac. Surg.* **2021**, *122*, 499–504. [CrossRef] [PubMed]
13. Glick, A.; Sista, V.; Johnson, C. Oral Manifestations of Commonly Prescribed Drugs. *Am. Fam. Physician* **2020**, *102*, 613–621. [PubMed]
14. Cavalcante, R.C.; Tomasetti, G. Pentoxifylline and tocopherol protocol to treat medication-related osteonecrosis of the jaw: A systematic literature review. *J. Craniomaxillofac. Surg.* **2020**, *48*, 1080–1086. [CrossRef] [PubMed]
15. On, S.W.; Cho, S.W.; Byun, S.H.; Yang, B.E. Various Therapeutic Methods for the Treatment of Medication-Related Osteonecrosis of the Jaw (MRONJ) and Their Limitations: A Narrative Review on New Molecular and Cellular Therapeutic Approaches. *Antioxidants* **2021**, *10*, 680. [CrossRef] [PubMed] [PubMed Central]
16. de Morais, R.P.L.; de Aguiar, A.W.P.B.; da Hora Sales, P.H.; Carvalho, A.A.T.; Vescovi, P.; Meleti, M.; Leão, J.C. Is the use of Pentoxifylline and Tocopherol effective in the treatment of Osteoradionecrosis of the jaws or for the treatment of medicationosteonecrosis of the jaw? An overview. *J. Stomatol. Oral Maxillofac. Surg.* **2023**, *125*, 101959. [CrossRef] [PubMed]
17. Isleyen, M.; Cina, M.; Asci, H.; Ilhan, I.; Oguz Yuceer, R. The Preventive Effect of Preoperative and Postoperative Selenium on the Medication-Related Osteonecrosis of the Jaw: An Animal Study in Rats. *J. Oral Maxillofac. Surg.* **2024**, *82*, 828–839. [CrossRef] [PubMed]

18. Delfrate, G.; Mroczek, T.; Mecca, L.E.A.; Andreis, J.D.; Fernandes, D.; Lipinski, L.C.; Claudino, M.; Franco, G.C.N. Effect of pentoxifylline and α-tocopherol on medication-related osteonecrosis of the jaw in rats: Before and after dental extraction. *Arch. Oral Biol.* **2022**, *137*, 105397. [CrossRef] [PubMed]
19. Scribante, A.; Gallo, S.; Pascadopoli, M.; Frani, M.; Butera, A. Ozonized gels vs chlorhexidine in non-surgical periodontal treatment: A randomized clinical trial. *Oral Dis.* **2024**, *30*, 3993–4000. [CrossRef] [PubMed]
20. Goswami, P.; Sharma, K.; Maiti, N.; Yadav, S.; Verma, V.; Puthenkandathil, R. Ozone: An Adjunct in Dental Treatment. *J. Pharm. Bioallied Sci.* **2024**, *16* (Suppl. S1), S2–S4. [CrossRef] [PubMed] [PubMed Central]
21. Goker, F.; Donati, G.; Gallo, F.; Sparaco, A.; Rania, V.; Busa, A.; Grecchi, F.; Grecchi, E.; Colapinto, G.; Del Fabbro, M. Ozone infiltration as an adjunctive treatment to piezoelectric surgery in the management of medication-related osteonecrosis of the jaws: Case series of 29 patients. *Oral Maxillofac. Surg.* **2024**, *28*, 1197–1207. [CrossRef] [PubMed]
22. Butera, A.; Pascadopoli, M.; Gallo, S.; Pérez-Albacete Martínez, C.; Maté Sánchez de Val, J.E.; Parisi, L.; Gariboldi, A.; Scribante, A. Ozonized Hydrogels vs. 1% Chlorhexidine Gel for the Clinical and Domiciliary Management of Peri-Implant Mucositis: A Randomized Clinical Trial. *J. Clin. Med.* **2023**, *12*, 1464. [CrossRef] [PubMed] [PubMed Central]
23. Silva, R.C.M.D.; Silva, L.G.C.D.; Cruz, N.T.D.S.; Barbosa, Á.R.L.; Maia, P.R.L.; Martins, A.R.L.A. Evaluation of two low-level laser techniques as an adjunct to basic periodontal therapy: A randomized clinical trial. *Lasers Med. Sci.* **2025**, *40*, 6. [CrossRef] [PubMed]
24. Scribante, A.; Gallo, S.; Pascadopoli, M.; Soleo, R.; Di Fonso, F.; Politi, L.; Venugopal, A.; Marya, A.; Butera, A. Management of Periodontal Disease with Adjunctive Therapy with Ozone and Photobiomodulation (PBM): A Randomized Clinical Trial. *Photonics* **2022**, *9*, 138. [CrossRef]
25. El-Halwagy, M.O.; Hegazy, E.M.; Shalaby, H.K.; Mahmoud, E.F. Impact of short and long-term application of low-level laser therapy on mandibular alveolar process of osteoporotic rats—A Histological and Molecular Study. *Lasers Med. Sci.* **2025**, *40*, 5. [CrossRef] [PubMed] [PubMed Central]
26. Jankowski, T.; Jankowska, A.; Palczewska-Komsa, M.; Jedliński, M.; Kazimierczak, W.; Janiszewska-Olszowska, J. Patient Experience and Wound Healing Outcomes Using Different Palatal Protection Methods After Free Gingival Grafts: A Systematic Review. *J. Funct. Biomater.* **2024**, *15*, 360. [CrossRef] [PubMed]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.