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Imaging aspects of maxillomandibular bone alterations in patients with multiple myeloma treated with bisphosphonates: A systematic review

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ABSTRACT

Purpose: Multiple myeloma (MM) is a rare cancer that is typically managed with bisphosphonates to slow bone resorption and prevent skeletal complications. This study aimed to identify imaging patterns in MM patients receiving bisphosphonate therapy.

Materials and Methods: This systematic review included studies investigating maxillomandibular bone alterations based on imaging examinations in MM patients treated with bisphosphonates. The selected studies were qualitatively assessed using the Critical Appraisal Tools from SUMARI.

Results: Six studies, involving 669 MM patients, were included, with 447 receiving bisphosphonate treatment. The majority were treated with pamidronate, zoledronate, or a combination of both. Seventy patients developed medication-related osteonecrosis of the jaw (MRONJ), predominantly in the mandible, characterized by the presence of bony sequestrum, bone sclerosis, increased periodontal ligament space, osteolytic lesions, and osteomyelitis as observed in imaging analyses. For non-MRONJ lesions, the mandible also exhibited the highest frequency of asymptomatic bone alterations. These ranged from "punched-out" osteolytic lesions or "soap bubble" lesions to solitary bone lesions, areas of bone sclerosis, abnormalities of the hard palate, osteoporosis, non-healed alveoli, and cortical bone rupture.

Conclusion: MM patients treated with bisphosphonates display radiographic patterns of maxillomandibular bone lesions. These patterns aid in diagnosis and facilitate early and targeted treatment, thereby contributing to improved morbidity outcomes for these patients. ***(Imaging Sci Dent 2024; 54: 221-31)***

KEY WORDS: Multiple Myeloma; Bisphosphonate; Bisphosphonate-Associated Osteonecrosis of the Jaw; Diagnostic Imaging

Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by the abnormal clonal proliferation of plasma cells within the bone marrow.[1] It has an annual incidence of approximately 178,000 new cases, and 117,000 deaths were reported in 2020, representing 1% of all deaths from malignancies and 10% to 15% of hematologic cancers.[2]

This disease exhibits a wide range of clinical manifestations, from asymptomatic cases to severe target organ damage. Notably, this includes hypercalcemia, renal failure, anemia, and bone lesions, collectively referred to by the acronym CRAB (calcium, renal, anemia, bone).[3] Bone lesions occur due to an imbalance in bone formation and resorption, leading to osteolytic lesions that may impact

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the spine, skull, and long bones. While gnathic bone lesions are commonly reported, they are not typically a primary manifestation of the disease.[4]

MM is incurable, but early diagnosis can prolong survival and improve patients' quality of life. The survival outcomes for patients with MM vary significantly. Therefore, the International Staging System has been established to offer a practical and objective method for predicting prognosis. This classification system utilizes the levels of β2-microglobulin and albumin to categorize MM patients into 3 stages: I, II, and III.[5] Oral manifestations in MM patients are nonspecific, but pain, bleeding, dysphagia, paresthesia, and osteolytic lesions are commonly reported.[4]

Immunosuppressive drugs, protease inhibitors, monoclonal antibodies, and drugs that inhibit bone resorption, such as bisphosphonates, are utilized in patient treatment depending on the disease stage.[5] Bisphosphonates curb the progression of osteoclastic activity and, when used in conjunction with antimyeloma drugs, increase bone mineral density. This combination helps reduce the incidence of bone fractures and pain. Since 2003, these medications have garnered significant attention in dentistry due to medication-related osteonecrosis of the jaw (MRONJ), a side effect predominantly linked to the use of intravenous nitrogen-containing bisphosphonates, including alendronate, ibandronate, pamidronate, risedronate, and zoledronate. However, the limitations of available data, primarily comprising clinical cases or case series, restrict the ability to establish a correlation between the stage of MM and the MRONJ pattern.[5,6]

In MM patients treated with bisphosphonates, certain radiographic findings frequently occur, including bone sclerosis, cortical surface irregularities, bone sequestration, and radiolucent lesions.[3,5] Although the occurrence of maxillomandibular lesions as an early sign is uncommon in MM patients, the concurrent use of bisphosphonates with the disease heightens the risk of gnathic lesions. This necessitates a differential diagnosis for maxillary lesions, particularly in elderly patients presenting with other symptoms. Early detection of these changes can significantly impact both the management and outcomes of the disease.[4]

Considering the importance of analyzing and detecting the pattern of bone lesions for identifying osteonecrosis associated with bisphosphonate use or bone remodeling due to cancer progression,[7] this systematic review investigated the imaging findings in MM patients undergoing bisphosphonate treatment.

Material and Methods

This systematic review was developed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[8] The protocol was registered on PROSPERO with the identification CRD420 21242279.

Study design and search strategy

The aim of this systematic review was to investigate published studies on maxillomandibular bone alterations in MM patients treated with bisphosphonates. The PECO question was structured as follows: P (participants) refers to patients with MM; E (exposure) involves treatment with bisphosphonates; C (control) includes MM patients not treated with bisphosphonates; O (outcome) denotes the presence of characteristics of maxillomandibular bone alterations, as observed through imaging examinations.

Studies were searched and identified in the following databases: PubMed (MEDLINE), Embase, Scielo, Web of Science, Science Direct, Scopus, and Lilacs. Additionally, literature from the first 10 pages of Google Scholar and searches on Open Grey were included. Duplicates were removed using Mendeley software.

The primary search strategy employed was follows: (((multiple myeloma OR smoldering multiple myeloma OR myeloma) AND ((“panoramic radiograph*” OR “panoramic dental radiograph*” OR “dental radiograph*” OR “dental digital radiograph*” OR “tooth radiograph*” OR “teeth radiograph*” OR orthopantomography* OR pantomograph* OR radiograph* OR “computed tomography” OR “cone beam computed tomography”))) AND (“maxillary bone lesions” OR jawbones OR mandible OR maxilla OR “gnathic bones” OR “jaw lesions” OR “mandibular bone” OR “maxillary bone”))) AND (“Bisphosphonate” OR “Bisphosphonate therapy”))).

Inclusion and exclusion criteria

All published studies that described changes in maxillomandibular bone in MM patients treated with bisphosphonates and evaluated through panoramic radiography were eligible. This included randomized controlled clinical trials, cohort studies, case-control studies, and cross-sectional studies. Excluded from this review were reviews, case reports, case series, letters, personal opinions, book chapters, and conference abstracts.

The use of panoramic radiographs in this study was supported by their established role in dentistry as a screening tool for identifying bone pathologies. This method is not

only cost-effective for patients but also offers a comprehensive view of the maxillofacial region. Additionally, recent evidence highlights its effectiveness in detecting various maxillary bone alterations in MM patients. These include solitary and multiple bone lesions, diffuse osteoporosis, diffuse sclerosis, abnormalities of the hard palate, and non-healing alveolar lesions. Consequently, panoramic radiography is indispensable for the clinical assessment and monitoring of this condition.[5]

Article selection and data collection

Two researchers independently reviewed the titles and abstracts of all the studies, selecting those that met the inclusion criteria. Both authors then assessed the selected articles in full. In the event of a disagreement, a third researcher was consulted to reach a consensus. The final selection was based on the articles that were read in full.

Two reviewers collaboratively gathered data from the selected articles, including the authors and study year, study design, number of participants, study and control groups, gender, ethnicity/skin color, average age, clinical staging, number of patients receiving bisphosphonate treatment, number of patients developing osteonecrosis, patients developing other osteolytic lesions, type of bisphosphonates received, and duration of bisphosphonate treatment. Additionally, they collected specific details on the clinical and imaging aspects of osteonecrosis and other osteolytic lesions, when available.

Qualitative and statistical analysis

The selected studies underwent qualitative assessment through the use of the Critical Appraisal Tools in SUMARI (System for the Unified Management, Assessment and Review of Information), as proposed by the Joanna Briggs Institute (JBI) for cross-sectional studies.[9]

The 1-sample t-test was conducted to determine if there were any differences in MM incidence between sexes, with a significance level set at 95%. It was not possible to assess differences between ages and treatment outcomes due to insufficient detailed information in the included studies. Statistical analyses were carried out using R software (R Core Team 2023, Vienna, Austria).

Results

Study selection and characteristics of included studies

The results of database searches yielded a total of 204 articles. Additional searches in other sources, including Google Scholar, Open Grey, and reference searches, produced 284 articles. After removing duplicates, 371 studies remained available for evaluation. These studies were initially assessed based on their titles and abstracts, leading to the selection of 16 articles for full review. Following a thorough reading, 6 studies were chosen for qualitative analysis.[5,10-14] Figure 1 illustrates the study selection flowchart.

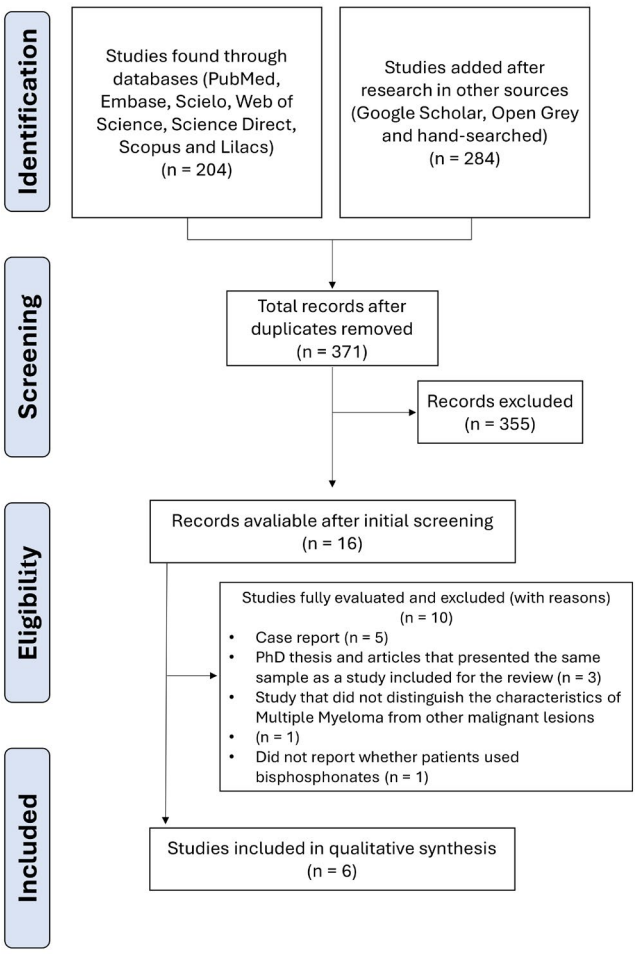

Fig. 1. Flowchart of study selection for review.

Among the studies included in this review, 2 were conducted in the United States,[10,12] 2 in Brazil,[5,13] 1 in Canada,[11] and 1 in Taiwan.[14] Only the Taiwanese research had a longitudinal design, occurring between 2010 and 2019. The other studies were retrospective cross-sectional research.

For comparison purposes, studies categorized patients into case and control groups. Three studies specifically included patients diagnosed with MRONJ in the case group.[10-12] The Brazilian studies grouped patients who underwent bisphosphonate treatment into the case group and

Table 1. General characteristics of the included studies on patients with multiple myeloma (MM)

Author/year and country	Study group and control group	Total number of included MM patients	Clinical staging	Number of MM patients treated with bisphosphonates	Patients who developed MRONJ	Age range (mean)	Sex	Skin color	Type of bisphosphonates received	Duration of treatment with bisphosphonates
Badros et al. (2006)[10] United States	SG: 22 patients with MM and MRONJ CG: 68 patients with MM without MRONJ	90	NI	84	22	Total: 27-78 years Mean: 58 years MRONJ 40-78 Mean: 61 years	Total: W: 27 M: 63 MRONJ: W:5 M: 17	Total: White: 60 Black: 28 Asian: 2 MRONJ White: 19 Black: 3 Asian: 0	Pamidronate: 17 (3 developed MRONJ) Zoledronate: 34 (2 developed MRONJ) Pamidronate + zoledronate: 33 (17 developed MRONJ) None: 6	NI
Jadu et al. (2007)[11] Canada	SG: patients with MRONJ CG: patients without MRONJ	120	NI	120	24	NI	NI	NI	Pamidronate	NI
Faria et al. (2018)[5] Brazil	SG: patients treated with Bisphosphonates CG: patients not treated with Bisphosphonates	188	DS staging: 1A (0) 1B (0) 2A (16) 2B (0) 3A (133) 3B (39)	88	0	31-90 SG: 63.5 CG: 64.9	105 M 83 W	NI	Pamidronate Zoledronate Pamidronate + zoledronate	0 to 12 months: 65 patients 12 to 24 months: 19 patients 24 to 36 months: 4 patients
Wazzan et al. (2018)[12] United States	SG: 16 patients with MRONJ CG: 100 patients without MRONJ	116	NI	87	16	Non-MRONJ: 61.30 (DP: 9.96) MRONJ: 63.69 (DP: 8.95)	Non-MRONJ: W: 59 M: 41 MRONJ W: 6 M: 10	NI	Zoledronate: 72 Pamidronate: 8 Others: 7	Non-MRONJ: approximately 1 year MRONJ: approximately 2 years
Rocha et al. (2020)[13] Brazil	SG: patients treated with bisphosphonates CG: patients not treated with Bisphosphonates	33	NI	23	NI	NI	NI	NI	NI	NI
Lu et al. (2021)[14] Taiwan	SG: patients with bone lesions CG: patients without bone lesions	122	DS staging: 1A (0)/1B (1) 2A (10)/2B (3) 3A (100)/3B (8) ISS staging: 1 (33) 2 (39) 3 (50)	45	8	45-86 years (69.9)	62 M 60 W	NI	Zoledronate	7 months to 3 years

NI: no information, MRONJ: medication-related osteonecrosis of the jaw, M: men, W: women, SG: study group, CG: control group, SD: standard deviation, ISS: International Staging System

Table 2. Characteristics of patients with multiple myeloma (MM) who developed medication-related osteonecrosis of the jaw (MRONJ)

Author/year and country	Disease status	Site	Clinical characteristics, signs, and symptoms	Number of lesions	Risk factors associated to MRONJ	Average time for resolution of MRONJ	Imaging characteristics of the gnathic bones post Bisphosphonates	Clinical management
Lu et al. (2021)[14] Taiwan	NI	Maxilla: 1 patient Mandible: 6 patients Maxilla and mandible: 1 patient	Bone pain, difficulty chewing, recurrent abscess with fistula, and exposure of necrotic bone	NI	Dental extraction: 3 patients Spontaneous development: 5 patients	8.7 months	Change in trabecular bone, increased bone density (osteosclerosis), increased periodontal ligament space and lamina dura, and focal bone sequestration	5 patients: surgery, antiseptic mouthwashes, and antibiotics
Jadu et al. (2007)[11] Canada	Progressive: 6 patients Non- progressive: 16 patients	Maxilla: 4 patients Mandible: 16 patients Maxilla and mandible: 4 patients	Pain, swelling, soft tissue lesion	Solitary: 19 patients Multiple: 4 patients	Macrotrauma: 15 patients Microtrauma: 2 patients Spontaneous development: 7 patients	NI	Bone sequestration, lytic lesions, and bone sclerosis	NI
Badros et al. (2006)[10] EUA	Recurrence: 16 patients Remission: 6 patients	Maxilla: 2 patients Mandible: 15 patients Maxilla and mandible: 5 patients	Pain, bone exposure (asymptomatic in some cases), intraoral purulent secretion, submental edema	NI	Dental extraction: 12 patients	NI	Lytic lesions, bone sclerosis with poorly defined margins, increased periodontal ligament space, blurring of the boundaries of the inferior alveolar canal, and an onion skin appearance in advanced cases (similar to Garre's osteomyelitis-ossifying periostitis).	14 patients: extensive debridement and bone sequestrectomy 4 patients: bone resection after several treatment failures 6 patients: antibiotics and removal of bone spicules

NI: no information

Table 3. Characteristics of patients with multiple myeloma (MM) with other bone alterations (not associated with medication-related osteonecrosis of the jaw)

Author/year and country	Number of patients with non-MRONJ bone lesions	Site	Anatomical regions affected	Size of the lesion	Clinical characteristics, signs, and symptoms	Imaging characteristics of the gnathic bones	Presence of osteoporosis	Comorbidities
Lu et al. (2021)[14] Taiwan	43 patients	Maxilla: 1 patient Mandible: 37 patients Maxilla and mandible: 5 patients	Mandible: Body, angle, ramus of the mandible, and condyles. Maxilla: Posterior teeth and the region of the tuber.	NI	Alveolar edema, dental mobility, and fistula.	Multiple small lesions with punched-out appearance, multilocular soap bubble lesions, single osteolytic lesions with irregular borders, pathological fractures, osteosclerotic lesions.	8 patients	NI
Rocha et al. (2020)[13] Brazil	33 patients	Maxilla: 87 alterations Mandible: 58 alterations	Maxila: Posterior region (106) Anterior region (36) Tuberosities (52) Maxillary sinuses (85) Nasal fossa (36) Nasopalatine canal (34) Teeth (41) Mandible: Condyles (63) Rami (70) Angles (67) Body (68) Symphysis (34) Mandibular canal (41) Mental foramen (37) Coronoid process (30) Teeth (34)	Maxilla with bisphosphonates ≥ 5 mm: 59 lesions ≤ 5 mm: 5 lesions Maxilla without Bisphosphonates ≥ 5 mm: 22 lesions ≤ 5 mm: 1 lesion Mandible with Bisphosphonates ≥ 5 mm: 42 lesions ≤ 5 mm: 2 lesions Mandible without Bisphosphonates: ≥ 5 mm: 13 lesions ≤ 5 mm: 1 lesion	NI	Non-sclerotic lesions, unilocular and multilocular osteolytic lesions, and cortical bone rupture.	NI	NI
Faria et al. (2018)[5] Brazil	188 patients	Maxilla: 242 alterations Mandible: 490 alterations		NI	NI	Solitary and multiple osteolytic lesions, diffuse osteoporosis, bone sclerosis, abnormalities of the hard palate, and non-healed alveolus after recent extraction	214 areas of osteoporosis in 188 patients	Hypertension (81) Diabetes mellitus (28) Heart disease (27) Depression (5) Renal insufficiency (10) Hyperparathyroidism (7) Hypothyroidism (4) Hepatitis (2)

NI: no information; MRONJ: medication-related osteonecrosis of the jaw

compared them to those who did not receive this treatment. Lu et al.[14] divided patients according to the presence or absence of maxillomandibular bone lesions.

In total, this review included 669 MM patients, of whom 447 received bisphosphonate treatment and 70 developed MRONJ. Three studies[5,13,14] that included a total of 343 individuals revealed 264 participants having additional maxillomandibular bone changes linked to MM (other studies did not include this information).

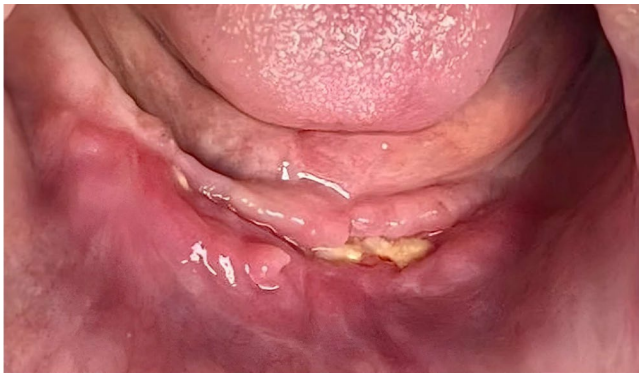

Fig. 2. Ulceration and necrosis of the oral mucosa in the anterior mandibular region associated with bisphosphonate use in a patient with multiple myeloma.

The age of the patients diagnosed with MM ranged from 31 to 90 years, with averages ranging between 58 and 69.9 years. In total, 298 (55.4%) MM patients were men, and 240 (44.6%) were women; however, this information was not available in the studies of Rocha et al.[13] and Jadu et al.[11] No statistically significant difference was noted in MM incidence between sexes ($p=0.06$, 1-sample t-test). Information on ethnicity/skin color was only available in one study,[10] which showed a higher frequency of MM in White individuals.

Most patients who received bisphosphonates were treated with pamidronate, zoledronate, or a combination of both. The duration of bisphosphonate treatment varied, ranging from 0 months to 3 years. All general information about the studies included in this review is described in Table 1.

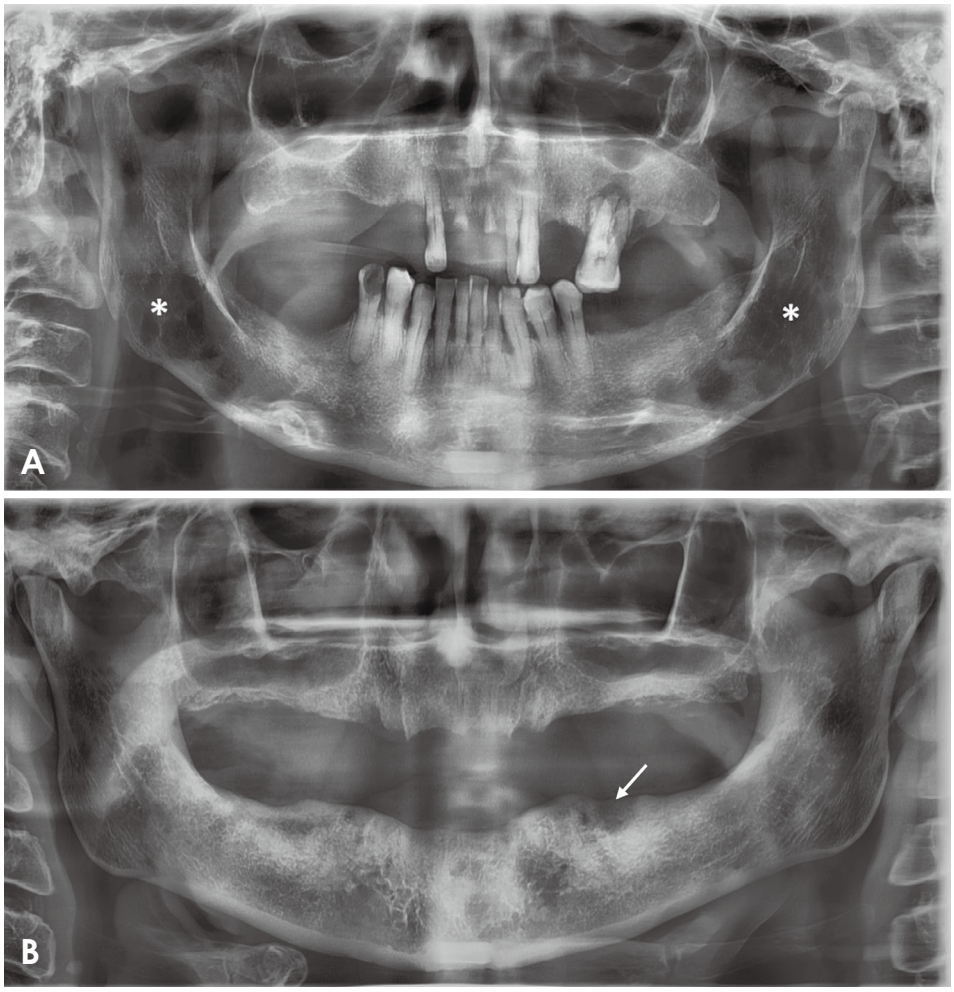

Fig. 3. Digital panoramic radiographic images of multiple myeloma patients. A. Multilocular non-corticalized osteolytic lesions in the region of the mandibular ramus and angle bilaterally (asterisk). B. Alteration of the bone trabeculation with areas of diffuse sclerosis in the mandible. The arrow points to a radiolucent area compatible with a recent extraction site or unhealed socket.

Table 4. Summary of scores for items of the Joanna Briggs Institute critical appraisal checklist for analytical cross-sectional studies

No.	Item	Frequency out of 6 (%)
01	Were the criteria for inclusion in the sample clearly defined?	5 (83.3%)
02	Were the study subjects and the setting described in detail?	5 (83.3%)
03	Was the exposure measured in a valid and reliable way?	6 (100%)
04	Were objective, standard criteria used for measurement of the condition?	6 (100%)
05	Were confounding factors identified?	5 (83.3%)
06	Were strategies to deal with confounding factors stated?	5 (83.3%)
07	Were the outcomes measured in a valid and reliable way?	6 (100%)
08	Was appropriate statistical analysis used?	6 (100%)

Characteristics of patients who developed MRONJ

The clinical and imaging characteristics of patients who developed MRONJ are detailed in Table 2. Among the 70 patients with osteonecrosis, 7 had lesions confined to the maxilla, 37 to the mandible, and 10 had lesions in both the maxilla and mandible. This information was not available in the study by Wazzan et al.[12]

Patients with MRONJ presented bone pain, edema, abscess, fistula, and bone exposure. Tooth extraction was associated with lesion development in most patients.

The most commonly reported imaging characteristics included the presence of bony sequestrum, bone sclerosis, and increased periodontal ligament space. Additionally, osteolytic lesions and osteomyelitis were observed. Clinical management across all studies involved surgical intervention and the use of antibiotics. Figure 2 depicts the clinical presentation of a mandibular lesion in an MM patient with MRONJ.

Characteristics of patients with other maxillomandibular bone alterations

The clinical and imaging characteristics of patients with other maxillomandibular bone alterations (non-MRONJ) are listed in Table 3.

Overall, the mandible was the region most commonly affected by bone alterations, which were predominantly asymptomatic. Lu et al.[14] observed that symptomatic lesions were early presentations of MM (plasmacytoma).

Radiographically, the alterations observed were varied, including "punched-out" osteolytic lesions, "soap bubble" lesions, solitary bone lesions, areas of bone sclerosis, abnormalities of the hard palate, osteoporosis, non-healed alveoli, and cortical bone rupture. Figure 3 illustrates some of the imaging alterations presented in this systematic review for MM patients.

Quality assessment

The JBI assessment checklist evaluates quality based on 8 items. The response options are "yes," "no," "unclear," and "not applicable," as appropriate. The percentage of studies meeting various assessment criteria was calculated and summarized. Four out of 8 quality criteria were met by all included studies (Table 4).

Discussion

One of the main complications of MM is the progression to bone disease, which has a direct impact on patient morbidity.[15] Despite the continuing development of new antiresorptive medications, bisphosphonates remain the standard treatment for MM.[5] Studies have demonstrated a close relationship between the use of bisphosphonates in MM patients and the appearance of radiographic changes in the maxilla and mandible. The present systematic review showed that MM patients exposed to bisphosphonates tended to present asymptomatic lesions in the mandible, MRONJ, and other bone alterations such as osteolytic lesions, osteosclerosis, osteoporosis, abnormalities of the hard palate and in alveolar healing, and cortical bone rupture.

After the development of more potent nitrogen-containing drugs, such as pamidronate and zoledronic acid, bisphosphonates have made significant improvements in the quality of life of patients with MM by reducing bone pain and preventing related skeletal events and hypercalcemia.[16,17] Pamidronate and zoledronate, which are second-generation bisphosphonates, play a crucial role in minimizing bone complications in MM, exhibiting higher bioavailability and lower elimination during bone resorption and remodeling than oral bisphosphonates.[5] According to the American Association of Oral and Maxillofacial Surgeons (AAOMS), zoledronic acid is the most commonly

used bisphosphonate in MM and carries a risk of developing MRONJ that is 2 to 10 times higher than that in cancer patients treated with a placebo.[12,18] This review found that most MM patients receiving bisphosphonates were treated with either pamidronate, zoledronate, or a combination of both, with treatment durations not exceeding 3 years.

This study also confirmed that in MM patients using bisphosphonates, the incidence of both MRONJ and non-MRONJ maxillomandibular bone lesions is predominantly higher in the mandible than in other locations. Osteolytic lesions tend to extend throughout the maxilla or mandible. Furthermore, the posterior region of the maxilla appears to be more affected than the anterior region, possibly due to increased bone resorption and remodeling processes following early tooth loss.[13]

Some authors have noted that the body, angle, and ramus of the mandible are the most frequently affected areas, suggesting that the mandible's higher affinity for bisphosphonate deposition compared to other bone sites may explain this phenomenon.[6] Lu et al.[14] showed that the presence of osteolytic lesions in the mandible has a negative impact on the survival of MM patients. These findings suggest that analyzing changes in the mandibular pattern through panoramic radiography could provide a quicker and simpler method for identifying MM patients with more aggressive disease, as opposed to detecting multiple focal lesions through magnetic resonance imaging of the spine and pelvis.[19] Additionally, various other factors affect the survival of individuals with MM, such as age and overall health,[14,19] underscoring the importance of understanding prognostic factors in MM for optimal patient care.

MM lesions in gnathic bones of patients exposed to bisphosphonates are often asymptomatic. In contrast, MRONJ typically presents with characteristic signs and symptoms such as bone pain, edema, abscess, fistula, and bone exposure, as highlighted in this systematic review. Dental extractions have been identified as the primary risk factor for MRONJ. Bacci et al.[20] reported that 44.4% of MM patients required dental extractions, predominantly due to periodontal disease. Research indicates that the development of MRONJ is triggered by local infections that necessitate dental extractions, rather than by the trauma of the extraction itself.[21,22] Moreover, Migliorati et al.[23] proposed that post-extraction healing is delayed in patients on bisphosphonate therapy. Although the precise pathogenesis of MRONJ still requires further investigation, it is clear that preventive dental consultations play a crucial role in the clinical management of MM patients undergoing BP therapy.

It is worth noting that the nonspecific radiographic features of MRONJ may overlap with those of MM, as demonstrated in this study, including bone sequestrations, bone sclerosis, increased periodontal ligament space, and osteolytic lesions. The differential diagnosis of MM lesions is challenging due to the variability in imaging presentations, which can mimic other malignant diseases, osteomyelitis, MRONJ, or common odontogenic lesions associated with teeth.[14,24]

It should be emphasized that although bisphosphonates are well-established drugs in MM treatment, with a good long-term safety profile and effectiveness in reducing bone diseases, their use presents adverse events and limitations, especially in patients with renal insufficiency.[7] The utilization of newer medications, such as denosumab (DENOS), is gaining momentum. The Bone Working Group of the International Myeloma Working Group recommends prioritizing DENOS over zoledronic acid in patients with renal dysfunction due to its lower risk of renal toxicity. This recommendation also extends to those with myeloma-related hypercalcemia, especially in individuals who are refractory to zoledronic acid. Additionally, they posit that DENOS may extend progression-free survival in newly diagnosed MM patients with MM-related bone disease who are eligible for autologous stem cell transplantation.[25] If long-term administration of DENOS is conclusively demonstrated to be safe and effective, it may eventually replace the use of bisphosphonates in MM therapy.[15]

Given that MRONJ is a potentially serious complication of intravenous bisphosphonates and denosumab, the Clinical Expert Panel of the American Society of Clinical Oncology recommends that the decision to continue a bone-targeted agent in the presence of MRONJ should be tailored to the individual. This decision should consider both the risk-benefit ratio and the severity of the bone disease. Furthermore, before initiating bone-modifying therapy, all patients should receive a comprehensive preventive dental evaluation. This includes treating any active oral infections and addressing sites at high risk for infection. Additionally, patients should maintain excellent oral hygiene and, if feasible, avoid invasive dental procedures during therapy.[26]

Several factors limit the conclusions that can be drawn from the results presented here. These include the limited number of studies focusing on gnathic bone alterations in MM patients treated with bisphosphonates, the lack of baseline radiographs, the absence of a defined minimum follow-up period for evaluating MRONJ lesions, and the fact that some included studies did not clearly exclude

patients who were using corticosteroids or had systemic diseases, which could confound the results. Despite these limitations, this systematic review enables a deeper understanding of maxillofacial findings in patients receiving intravenous bisphosphonates. It identifies radiographic patterns of maxillomandibular bone lesions that can assist in the early diagnosis of MM and suggests that bisphosphonates may primarily induce these alterations. Consequently, detecting these osteolytic lesions can guide treatment decisions, even in the absence of other clinical manifestations, underscoring the importance of a thorough analysis of the imaging characteristics of these lesions.

In summary, this systematic review indicates that bone alterations in MM patients treated with bisphosphonates are more frequently observed in the mandible than in other locations, are often asymptomatic and display a variety of radiographic patterns. These patterns range from MRONJ to "punched-out" osteolytic lesions, "soap bubble" lesions, solitary bone lesions, areas of bone sclerosis, abnormalities of the hard palate, osteoporosis, non-healed alveoli, and cortical bone rupture. Consequently, continuous and coordinated patient-centered multidisciplinary care is essential for diagnostic investigation and treatment planning. This approach aims to prioritize not only the longevity of MM patients but also their quality of life. Further clinical trials and laboratory investigations into the bone mechanisms of bisphosphonates are necessary to improve researchers' understanding of maxillomandibular trabecular bone evaluation.

Conflicts of Interest: None

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