Imaging Science in Dentistry 2024; 54: 211-20
https://doi.org/10.5624/isd.20230257

Beyond the mouth: Uncovering non-secretory multiple myeloma through oral symptoms

Pedro Henrique Chaves Isaias[1,*], Fábio Wildson Gurgel Costa[1], Pedro Henrique Gonçalves Holanda Amorim[2], Raul Anderson Domingues Alves da Silva[3], Fabrício Bitu Sousa[1,3], Karuza Maria Alves Pereira[1], Ana Paula Negreiros Nunes Alves[1], Mário Rogério Lima Mota[1]

[1]*Department of Dental Clinic, Postgraduate Program in Dentistry, Federal University of Ceará, Fortaleza, Ceará, Brazil*
[2]*Department of Dentistry, Catholic University Center of Quixadá, Quixadá, Ceará, Brazil*
[3]*Department of Dentistry, Christus University Center, Fortaleza, Ceará, Brazil*

ABSTRACT

Non-secretory multiple myeloma (NSMM) is a rare cancer of plasma cells characterized by the absence of detectable monoclonal M protein in the blood or urine. A 57-year-old woman presented with mandibular pain but without intraoral swelling. Imaging studies revealed multiple osteolytic lesions in her mandible and pronounced root resorption of the left mandibular second molar. Biopsy results showed atypical plasmacytoid cells positive for anti-kappa, CD138, MUM1, and CD79a antibodies, but negative for anti-lambda and CD20. These results were indicative of a malignant plasma cell neoplasm. No abnormalities were revealed by free light chain assay or by serum or urine protein electrophoresis, leading to a diagnosis of NSMM. The patient began chemotherapy in conjunction with bisphosphonate therapy and achieved remission following treatment. This case underscores the critical role of dentists in the early detection and prevention of NSMM complications, as the disease can initially present in the oral cavity. ***(Imaging Sci Dent 2024; 54: 211-20)***

KEY WORDS: Multiple Myeloma; Jaw; Radiography, Panoramic; Immunohistochemistry

Multiple myeloma (MM) is a hematological cancer characterized by the uncontrolled proliferation of clonal malignant plasma cells within the bone marrow. This proliferation causes the overproduction of either intact immunoglobulins or non-functional immunoglobulin chains.[1] These plasma cells produce monoclonal antibodies known as M proteins, which can be detected in the serum or urine of patients with MM. M proteins consist of either kappa or lambda light chains, with or without associated heavy chains, and can cause damage to various target organs.[2,3] MM represents approximately 10% of all hematological malignancies.[1] In 2020, the global incidence of MM was 1.8 cases per 100,000 people, with a mortality rate of 1.1 deaths per 100,000 individuals.[4]

The presentation of MM can vary depending on the site of proliferation, with effects observed primarily in the bones along with systemic symptoms resulting from an excess of plasma cells in the bloodstream. The accumulation of immunoglobulins and the interaction of aberrant monoclonal plasma cells (via M protein) with other cells in the bone marrow can lead to various complications. These include hypercalcemia, renal insufficiency, anemia, and bone lesions (referred to as the CRAB criteria), as well as infections, fatigue, and pain.[5] In approximately 3% to 5% of patients who meet the criteria for MM diagnosis, no measurable M protein can be detected in the serum or urine. This variant of MM is known as non-secretory multiple myeloma (NSMM). Despite the absence of monoclonal gammopathy, NSMM typically exhibits the same clinical and radiological characteristics associated with

Received November 29, 2023; Revised February 6, 2024; Accepted February 14, 2024
Published online April 1, 2024
*Correspondence to : Prof. Pedro Henrique Chaves Isaias
Division of Oral Pathology, Department of Dental Clinic, Faculty of Pharmacy, Dentistry, and Nursing, Federal University of Ceará, Monsenhor Furtado Street, without number - Rodolfo Teófilo - 60430-350 - Fortaleza - CE, Brazil
Tel) 55-85-3366-8404, E-mail) ph.isaias@yahoo.com.br

Imaging Science in Dentistry · pISSN 2233-7822 eISSN 2233-7830

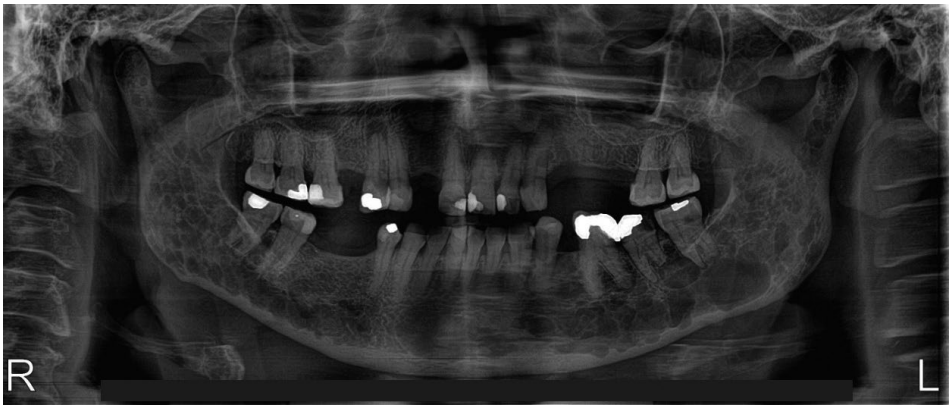

Fig. 1. Initial panoramic radiograph revealing extensive radiolucent areas in the mandible.

conventional MM.[6,7] However, NSMM presents the additional challenge of a lack of secreted immunoglobulins such as IgG, IgA, IgM, or kappa or lambda light chains. This absence of common markers in the blood and urine complicates diagnosis and monitoring.[8]

The interaction between malignant plasma cells and stromal cells (the supportive tissue of organs) within the bone marrow triggers a cascade of cytokine production that disrupts the balance between osteoclasts and osteoblasts. Consequently, osteoclastic activity is heightened, while osteoblastic activity is diminished. This disruption leads to the development of bone erosion areas, which give rise to lytic lesions—a hallmark of MM.[3,9,10] In patients with MM, these changes are frequently observed in skeletal regions including the vertebral column, femur, ribs, humerus, pelvis, and skull. However, jaw lesions have also been documented, and in some cases, these may represent the first detectable sign of the disease.[3,9,11,12]

Oral and jaw lesions can appear in up to 70% of patients with MM, with the mandible affected in approximately 35% of cases. Common signs and symptoms include pain, tooth loss, paresthesia, and gingival swelling.[13] However, the presence of these lesions as an early indicator of the disease is relatively rare and is more often associated with disease progression.[3,12] Reports of NSMM involving the maxillary bones are even scarcer,[6,14-16] and to date, no cases have been detailed as originating from mandibular involvement. The present report details a case of NSMM in which the initial findings were identified during dental consultation.

Case Report

This case report received approval from the Research Ethics Committee of the Federal University of Ceará, under opinion number 5.911.846. The patient provided her free and informed consent. A 57-year-old woman presented to the dental clinic, reporting severe, generalized pain on the left side of her jaw. She also noted decreased sensitivity in certain teeth and the surrounding gum tissue. No facial alterations or asymmetry were detected during the extraoral examination. Intraoral clinical examination revealed teeth with extensive restorations, some of which exhibited recurrent caries. The oral mucosa and alveolar structure appeared normal, with no deviations from the expected pattern. The patient was unaware of having any systemic diseases and was not taking any daily medications. To obtain a more thorough assessment, a panoramic radiograph was requested (Fig. 1).

Panoramic radiography revealed several multilocular osteolytic lesions in the mandible, each with a "punched-out" appearance. Erosion of the bilateral mandibular cortex was also evident, as was significant external root resorption at the distal root of the lower left second molar (tooth 37) and the lower left third molar (tooth 38). Given these bone changes, a cone-beam computed tomography (CBCT) scan was requested. From various angles, CBCT imaging displayed multiple hypodense areas in the mandible indicative of medullary and cortical bone erosion, which also presented a "punched-out" appearance. Notably, the scan showed no indication of volume augmentation in the buccolingual direction on the axial view (Fig. 2A). Furthermore, the coronal reconstruction revealed a clear rupture of the lingual cortical layer near tooth 37 (Fig. 2B), without signs of vertical volume expansion toward the base of the mandible.

Following the imaging evaluation, the clinical diagnosis was suggestive of a neoplasm of lymphoid origin, such as MM or lymphoma, or a metastatic process that necessitated further investigation. The differential diagnosis included ameloblastoma, osteosarcoma, Paget disease, or other fibro-osseous conditions, due to the presence of lytic le-

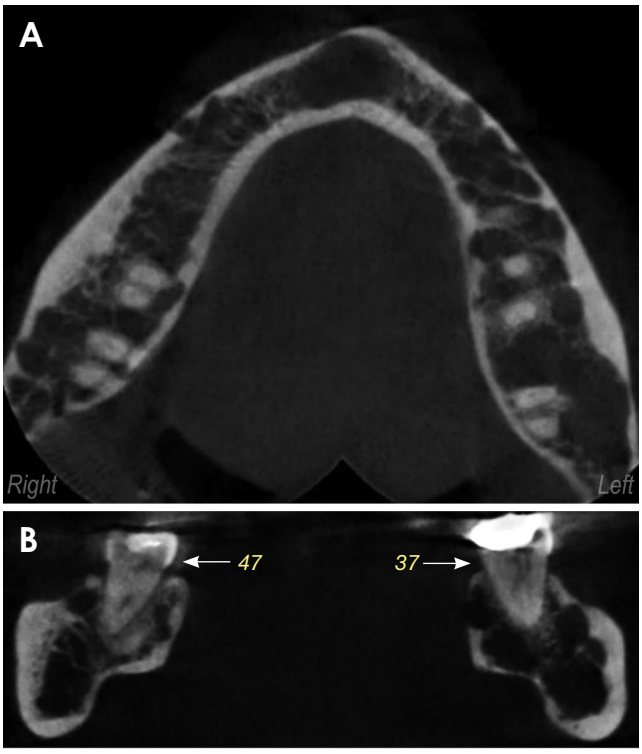

Fig. 2. A. Axial section of the initial computed tomography scan reveals several hypodense osteolytic regions in the mandible. These regions exhibit a distinct "punched-out" appearance and demonstrate no increase in volume in the buccolingual direction. B. A rupture in the lingual cortical layer is evident near the left mandibular second molar. Notably, the coronal reconstruction displays no signs of an increase in vertical volume towards the base of the mandible.

sions that can share radiographic characteristics with the primary conditions under consideration. An incisional biopsy of the mandible was performed, with samples taken from various areas including the left angle near tooth 37, the anterior region, and the right angle. Macroscopically, the biopsy fragments were firm and elastic with irregular shapes and surfaces, exhibited a brownish hue, and had a softened texture. The cut surfaces of the fragments appeared compact and similarly brownish.

Histopathological analysis revealed plasmacytoid cells forming diffuse and uniform layers (Figs. 3A and B) and which displayed varying degrees of differentiation, including eccentric nuclei and punctate chromatin (Fig. 3C). These cells had replaced the fibrovascular connective tissue and bone marrow. Immunohistochemical analysis indicated intense and diffuse positivity for anti-kappa (Fig. 3D), anti-CD138 (Fig. 3E), and anti-MUM1 (Fig. 3F) antibody in the plasmacytoid cells. Additionally, weak and sparse staining was noted for anti-CD79a antibody (Fig. 3G), while anti-lambda (Fig. 3H) and anti-CD20 (Fig. 3I) staining was negative. These histopathological findings were consistent with a diagnosis of plasma cell neoplasm. Given the diffuse bone lesions observed in the jaw, MM was suspected.

The patient was referred to an oncology and hematology service for investigation of the potential underlying condition. Over approximately 19 weeks, 2 hematological exams were performed. Complete blood count parameters, including an erythrogram, leukogram, and platelet count, consistently remained within normal ranges. These results showed no evidence of anemia or a meaningful drop in baseline hemoglobin levels. Additionally, serum calcium levels were within reference limits, with no signs of hypercalcemia.

However, clear changes were observed in other parameters, as illustrated in Table 1. Specifically, the patient's creatinine levels increased, exceeding the reference range, while beta-2 microglobulin levels remained elevated above reference values. Moreover, the estimated glomerular filtration rate (eGFR) decreased, indicating a moderate to severe reduction in kidney function. Notably, the results of protein electrophoresis remained within expected patterns, with no observed increases in the gamma fraction.

A posteroanterior chest X-ray of the patient's right side revealed multiple radiolucent areas with a "punched-out" appearance in the right humerus, clavicle, scapula, and ribs. These pathological patterns were not identifiable on an examination conducted 2 years and 4 months earlier for a different diagnostic purpose, rendering the presence of the disease at that time inconclusive (Figs. 4A and B). Bone densitometry revealed a 13% loss of bone mass in the lumbar spine region (segments L1-L4), suggestive of osteopenia.

Due to the lack of conclusive hematological and imaging findings, the patient continued to undergo diagnostic investigations. During this time, she sustained a fracture in the distal segment of the left clavicle following a sudden movement at home, with a pathological origin suspected. Radiographic examination of the area revealed radiolucent areas with a "punched-out" appearance in both the left clavicle and humerus (Fig. 4C).

A computed tomography (CT) scan of the skull, axial skeleton, and peripheral regions was performed as part of the evaluation for MM. The CT scan revealed numerous lytic lesions in various bones throughout the body. The affected areas included the skull, specifically the frontal bone, parietal bones, skull base, and facial bones, as well as the ribs, sternum, clavicles, scapulae, humeri, radii, cervical spine (particularly from C2 to C5), thoracic and lumbar spine (particularly from D9 to D11), iliac bones,

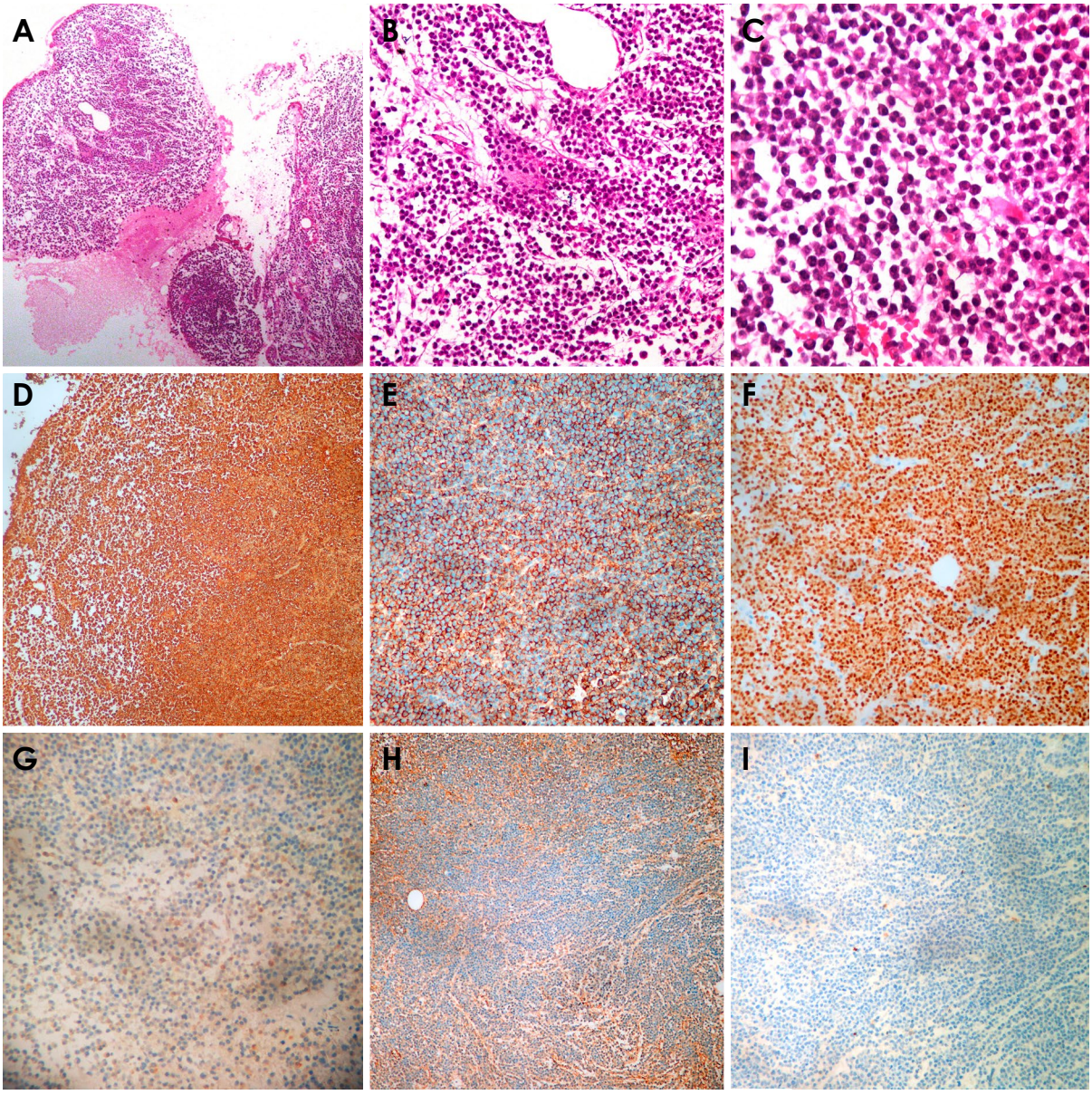

Fig. 3. A. Photomicrograph displaying cellular proliferation invading and replacing the sparse fibrous connective tissue and bone marrow (hematoxylin and eosin, ×50 magnification). B. This proliferation is characterized by diffuse and uniform layers of plasmacytoid cells (hematoxylin and eosin, ×200 magnification). C. The plasmacytoid cells exhibit varying degrees of differentiation, some with eccentric nuclei and punctate chromatin (hematoxylin and eosin, ×400 magnification). D. The cells displayed positivity for the anti-kappa antibody (immunohistochemical stain, ×50 magnification). E. Anti-CD138 positivity was also evident (immunohistochemical stain, ×200 magnification). F. The plasmacytoid cells tested positive for anti-MUM1 (immunohistochemical stain, ×100 magnification). G. Positivity for anti-CD79a was additionally observed (immunohistochemical stain, ×100 magnification). H. The plasmacytoid cells did not exhibit positivity for the anti-lambda antibody (immunohistochemical stain, ×50 magnification). I. The plasmacytoid cells stained negative for the anti-CD20 antibody (immunohistochemical stain, ×100 magnification).

sacral vertebrae, femurs, tibias, and fibulas. The widespread nature of these lesions strongly indicated the presence of MM.

Since protein electrophoresis did not reveal the presence of M protein, an additional test was performed to measure serum free light chain levels; however, these results were also not indicative of disease. The free kappa light chain level was 12.2 mg/dL, which falls within the normal reference range of 6.70 to 22.40 mg/dL. The free lambda light chain level was 16.9 mg/dL, also within the normal reference range of 8.30 to 27.00 mg/dL. Furthermore, the kappa/lambda ratio was 0.72, which is within

Table 1. Results of hematological parameters

	Initial hematological examination	Six weeks after initial examination	Reference range
Creatinine	0.7 mg/dL	1.40 mg/dL	Women over 12 years old: 0.6 to 1.1 mg/dL
Beta-2 microglobulin	2.75 mg/L	2.46 mg/L	1.00 to 2.40 mg/L
Estimated glomerular filtration rate	>90 mL/min/1.73 m^2	41.7 mL/min/1.73 m^2	Normal: >90 mL/min/1.73 m^2 Moderate to severe reduction: 30-44 mL/min/1.73 m^2
Protein electrophoresis			
Albumin	4.10 g/dL	4.40 g/dL	3.24 to 5.28 g/dL
Alpha 1	0.30 g/dL	0.29 g/dL	0.08 to 0.43 g/dL
Alpha 2	1.10 g/dL	0.71 g/dL	0.55 to 1.10 g/dL
Beta	1.30 g/dL	0.83 g/dL	0.52 to 1.15 g/dL
Gamma	1.00 g/dL	0.78 g/dL	0.64 to 1.54 g/dL

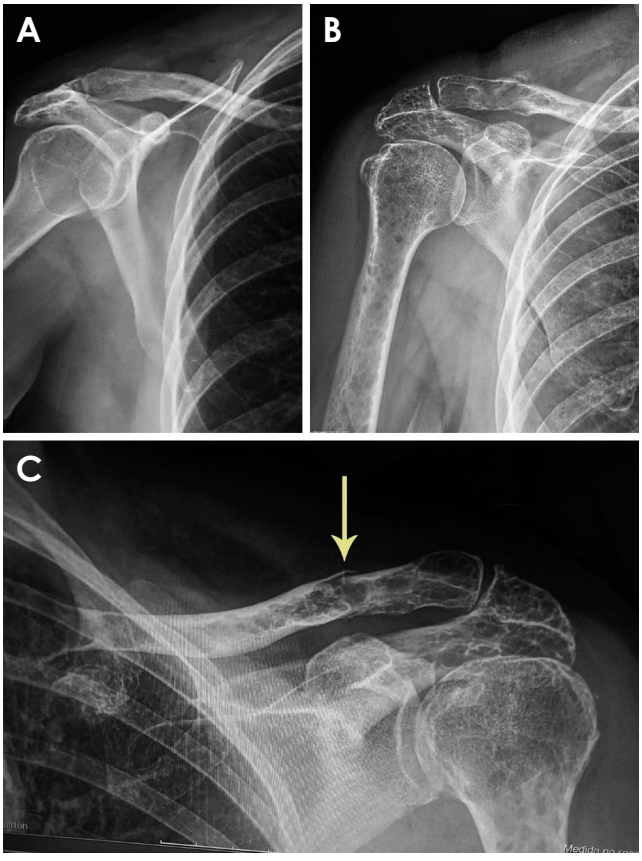

Fig. 4. A. Initial posteroanterior chest X-ray of the patient showing normal imaging characteristics on the right side. B. After 28 months, radiolucent areas with a "punched-out" appearance were observed in the same region, disseminated across the right humerus, clavicle, scapula, and ribs. C. On the patient's left side, another radiograph revealed an impacted fracture at the acromial end of the left clavicle (arrow), accompanied by lytic lesions scattered throughout the scapula, humerus, clavicle, and ribs.

the reference range of 0.31 to 1.56.

Considering the presence of disseminated bone lesions, the results of the incisional biopsy, and the absence of detectable M protein, a diagnosis of NSMM was established. The patient began a treatment regimen consisting of 6 cycles of chemotherapy in combination with steroids. The chemotherapy protocol included cyclophosphamide, bortezomib (Velcade), ondansetron (Nausedron), and dexamethasone (Decadron). Prior to the initiation of pamidronate therapy, the patient's left mandibular second molar was extracted. Pamidronate therapy was introduced 1 month after the extraction, once the healing was deemed satisfactory.

Throughout the course of treatment, hematological findings–including complete blood count parameters, calcium levels, and protein electrophoresis results–consistently remained within reference ranges. Creatinine and eGFR levels normalized, with no notable changes observed on blood or urine protein electrophoresis. One year following the incisional biopsy of the mandible, follow-up panoramic radiography was performed (Fig. 5A). Clinically and radiographically, the examination revealed satisfactory healing at the site of the extracted tooth 37 and apparent stabilization of the multilocular osteolytic lesions in the maxillae (Figs. 5B and C). Additionally, posteroanterior and lateral skull radiographs (Fig. 6) displayed a bone pattern indicative of osteoporosis in the cranial vault, as well as disseminated osteolytic lesions in the mandible. The patient completed a course of chemotherapy in combination with bisphosphonates, resulting in disease remission. She is currently awaiting an autologous bone marrow transplant as part of ongoing management.

Discussion

MM can be asymptomatic or present with nonspecific

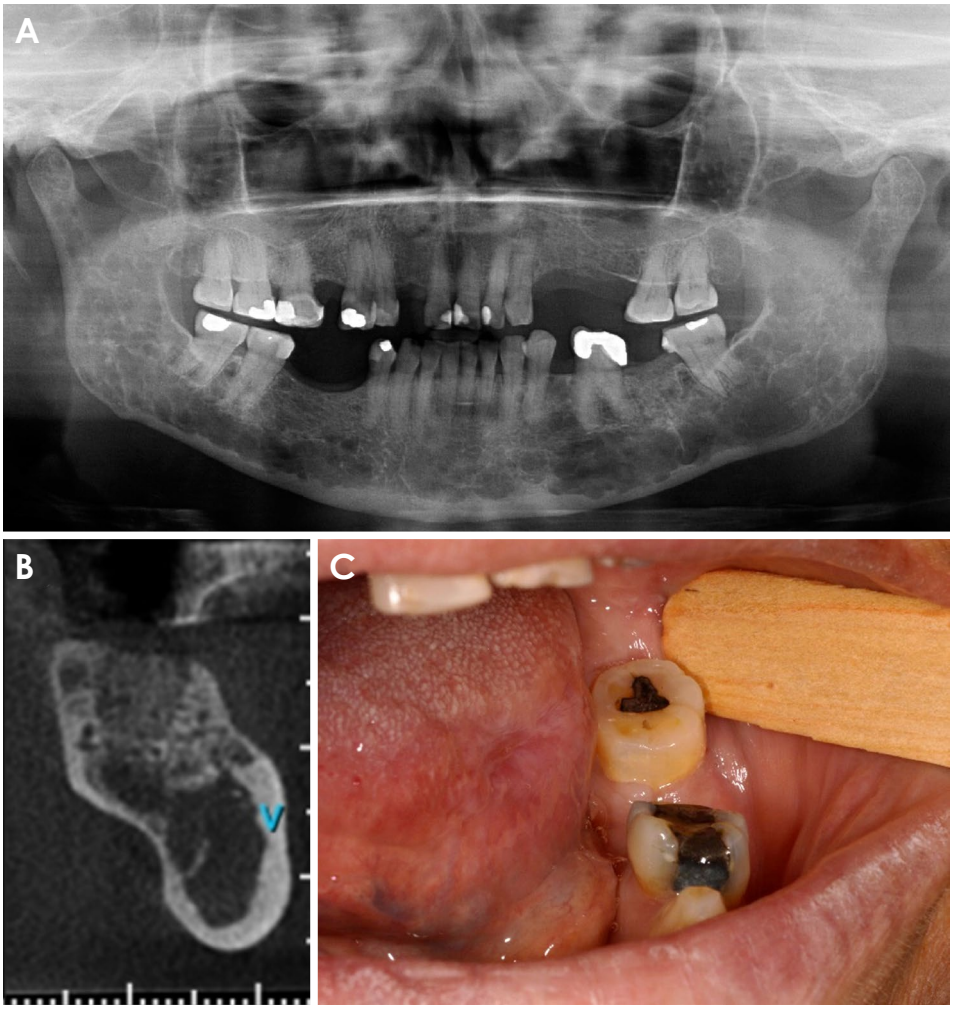

Fig. 5. A. Panoramic radiograph obtained following the extraction of the lower left second molar and chemotherapy for non-secretory multiple myeloma, showing satisfactory healing at the extracted tooth socket site. B. Parasagittal section of cone-beam computed tomography demonstrating the resolution of the previously noted cortical disruption in the region of the extracted lower left second molar. C. The mucosa appeared clinically normal, with no signs of exposed bone.

symptoms such as bone pain, anemia, fatigue, and osteolytic skeletal lesions, particularly in the early stages.[3] Moreover, in a small percentage of cases, monoclonal serum and urinary gammopathy may go undetected, further complicating the diagnostic process. These cases are designated as NSMM.[7] This report presents a compelling case of NSMM, initially identified based on jawbone lesions associated with nonspecific mandibular pain and inconclusive laboratory results.

When B cells transform into abnormal plasma cells, they produce large quantities of an abnormal antibody (a monoclonal immunoglobulin), termed the M protein. This protein is detectable in the blood and urine. In certain cases, these cells may not produce the complete immunoglobulin, instead releasing only the light chains–known as Bence-Jones proteins–into the bloodstream.[9,17] Malignant plasma cells can interact with the bone marrow stroma and an extensive network of cytokines, potentially leading to osteolytic destruction, extramedullary expansion, or the formation of soft tissue plasmacytomas.[18] The present case involved bone involvement in various parts of the skeleton; however, no extramedullary or soft tissue lesions were observed, underscoring the need for thorough investigation.

The International Myeloma Working Group updated the diagnostic criteria for MM in 2014, incorporating validated biomarkers alongside the traditional CRAB features (hypercalcemia, renal insufficiency, anemia, and bone lesions). A current MM diagnosis may include 1 or more CRAB features, which signify organ damage, as well as either the presence of clonal plasma cells in the bone marrow at a level of 10% or higher, or biopsy confirmation of a bone or extramedullary plasmacytoma. Clonality should be established by demonstrating kappa or lambda light chain restriction using flow cytometry, immunohistochemistry, or immunofluorescence.[19] Although bone lesions–including a pathological fracture–were evident in the present case, neither hypercalcemia nor anemia were observed. However, signs of renal involvement were evident, as

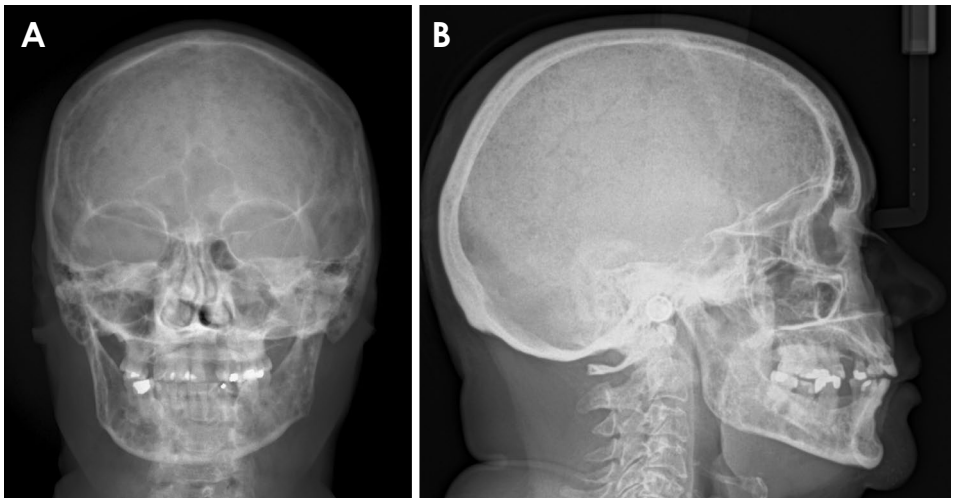

Fig. 6. A. Posteroanterior skull radiograph revealing osteoporosis in the cranial vault, with evident osteolytic involvement of the mandible. B. Lateral skull radiograph displaying the same osteoporotic features in the cranial vault, as well as osteolytic involvement of the mandible.

indicated by elevated creatinine levels and reduced eGFR. The diagnostic criteria for MM were fulfilled based on the presence of multiple bone lesions (a CRAB criterion) and the confirmation of monoclonality via bone biopsy. Nevertheless, the diagnosis was complicated by the absence of detectable M protein.

MM cells produce monoclonal immunoglobulins, which are detectable through serum or urine protein electrophoresis. In patients with MM, protein electrophoresis typically reveals an M protein spike in the γ (gamma) region, in addition to the albumin peak. However, in rare cases, such as with NSMM, the absence of monoclonal proliferation can complicate the diagnosis due to the lack of monoclonal gammopathy.[20,21] In the present case, serum and urine protein electrophoresis did not reveal the characteristic changes associated with MM. Consequently, when NSMM is suspected, it is important to conduct serum-free light chain analysis, as this technique can quantify free kappa and lambda chains at very low concentrations, even when monoclonal protein levels are undetectable by protein electrophoresis and immunofixation. If the values remain within the normal range, a diagnosis of NSMM should be considered. In this report, the serum free light chain ratio was found to be normal.[7]

NSMM typically presents with clinical and radiological characteristics similar to those of conventional MM,[6] which may include bone pain, pathological fractures, and amyloidosis.[1,22] The areas of bone involvement are usually those with high bone marrow content, including the skull, spine, sternum, vertebrae, pelvis, and hips. The maxillary bones are affected in approximately 30% of cases, with osteolytic lesions being the most common oral findings.[18,23,24]

Oral manifestations are often considered indicators of disease progression in both MM and NSMM, although they rarely represent initial signs of the disease. However, some published reports have identified oral manifestations as initial clinical signs of the condition. This includes intraoral swelling with osteolytic lesions in the jaws,[3,9,11,23,25-27] jawbone lesions without swelling,[28] involvement of the mandibular condyle,[29,30] and even soft tissue lesions without maxillary involvement.[31] In the early diagnostic stages of the present case, the first lesions observed were in the mandibular bone and were associated with pain and reduced sensitivity, but with no swelling or changes in the oral mucosa.

The English-language literature on oral manifestations and maxillary involvement in NSMM is sparse. Whicher et al. (1975) identified NSMM in a 69-year-old woman who presented with left shoulder pain, with further investigation revealing osteolytic lesions in the skull, mandible, humerus, and femurs.[15] Gray et al. (1997) described a 56-year-old woman with a secondary NSMM lesion in the left maxillary tuberosity; the patient experienced pain and mucosal swelling, with radiographic evidence of bone loss in the affected area.[16] Neeravari et al. (2011) reported the case of a 23-year-old woman with NSMM who presented with bilateral lower limb weakness and severe osteoporosis in the vertebral column, as well as multiple lytic lesions in the skull and mandible.[6] Lee et al. (2022) documented a case involving a 36-year-old man with NSMM, who exhibited facial swelling, nasal congestion, and cough. Imaging revealed lesions in the left main bronchus and the left maxilla, which presented as multiple extramedullary plasmacytomas.[14] In several cases of women between 23 and 69 years old, the mandible exhibited greater involve-

ment than the maxilla,[6,15,16] similar to the present case. Remarkably, in none of these cases was NSMM investigation initiated through dental evaluation or in response to mandibular lesions, underscoring the rarity of this report.

Radiographically, NSMM is characterized by the presence of multiple well-defined lytic lesions with non-sclerotic borders, creating a distinctive "punched-out" appearance. Conventional radiography has limitations, as it can only visualize lytic lesions when 30% to 50% of the trabecular bone has been eroded. Furthermore, differential diagnosis should consider other pathological processes of the maxilla, including ameloblastoma, osteosarcoma, and Paget disease.[3,24,32,33] Ameloblastoma often presents as a slow, painless growth of bone, despite its multilocular appearance and association with tooth resorption.[34] Osteosarcomas range from osteogenic (characterized by a sunburst appearance) to lytic or a combination of both, with potential widening of the periodontal ligament space in cases involving the mandible.[35] Paget disease of bone progresses from a "frosted glass" appearance to a "cotton wool" presentation.[36] These features differentiate it from the present case, underscoring the importance of careful diagnostic consideration. Across the array of imaging modalities available, whole-body low-dose CT (WBLDCT) is recommended; if this does not reveal signs of bone destruction, axial skeleton magnetic resonance imaging or positron emission tomography-CT should be considered.[32] In the case presented, WBLDCT was instrumental in supporting the diagnosis by revealing extensive bone involvement.

In cases of suspected MM or NSMM, histological analysis must be performed. Histologically, these neoplasms typically exhibit a diffuse proliferation of plasma cells characterized by cellular and nuclear pleomorphism. These cells may display hyperchromatism and often contain 2 or more nuclei; they also have abundant eosinophilic cytoplasm and an altered nucleus-to-cytoplasm ratio. Cells with plasmablastic features, such as large size and nuclear pleomorphism, may be observed. The differential histological diagnosis can include diffuse large B-cell lymphoma and plasmablastic lymphoma. To confirm the diagnosis of MM or NSMM, it is imperative to establish the monoclonality of the plasma cells, which can be achieved through immunohistochemical analysis.[3,37-39]

Monoclonality of neoplastic plasma cells is characterized in immunohistochemistry by light chain restriction, meaning that the tumor cells react to only 1 type of antibody that targets the light chain components of the immunoglobulin molecule (either kappa or lambda). Although extremely rare, MM can present with a single clone expressing both light chains. The tumor cells also demonstrate positivity for B-cell markers associated with the post-germinal center and plasma cells, such as anti-CD138, anti-CD38, and anti-MUM-1 antibodies, while they typically test negative for anti-CD20.[37,40] In the present case, the histological and immunohistochemical analyses conducted on the incisional biopsy of the mandible, along with the clinical and imaging findings, were consistent with NSMM.

Currently, NSMM has no known cure. However, a combination of chemotherapy and autologous stem cell transplantation has enabled many patients to achieve stable remission for several years. The treatment for NSMM follows the same regimen as for conventional MM, often involving the VD protocol, which combines bortezomib (Velcade) and dexamethasone. The addition of cyclophosphamide, doxorubicin, or thalidomide (VTD) may increase the regimen's effectiveness. Additionally, bisphosphonates are used to manage hypercalcemia and to modulate bone disease. Pain management generally includes opioid analgesics and nonsteroidal anti-inflammatory drugs, with radiation therapy considered for localized bone lesions.[1,7] In the present case, the patient was treated with the VD protocol and received pamidronate, an antiresorptive agent from the bisphosphonate class, which led to disease remission.

Individuals with NSMM require comprehensive oral care, ongoing education, and regular monitoring of their oral health to prevent complications, including medication-related osteonecrosis of the jaw (MRONJ). Consequently, invasive dental procedures should ideally be performed at least 4 weeks prior to starting antiresorptive medications. Patients should be informed of the potential signs of MRONJ, such as exposed bone and mandibular paresthesia.[13] Notably, the patient in this case did not develop MRONJ following the extraction of tooth 37.

This report presents a case of mandibular bone lesions associated with NSMM, which were identified as the first sign of the disease despite the absence of changes in the oral mucosa. Although initial manifestation of NSMM in the jawbones is uncommon, this case highlights the key role of imaging studies and biopsies for detecting systemic disease in early or advanced stages. This is particularly important given the frequency of nonspecific clinical findings and absence of distinctive laboratory markers, which can complicate diagnosis. For future management, panoramic radiographs or CBCT are recommended for the ongoing monitoring of jaw lesions to detect any indications of disease progression. It is also advisable to pro-

mote oral health through dental treatment prior to initiating oncologic therapy, thus reducing the risk of complications such as infections or MRONJ. This case provides a deeper understanding of NSMM and underscores the need to consider it within the differential diagnosis when encountering multiple osteolytic lesions of the jaw.

Conflicts of Interest: None

Acknowledgments

This case was presented as a poster at the 40th Annual Meeting of the Brazilian Society of Dental Research (SBPqO) in 2023 and was awarded first place in the Case Reports and Reviews Panel category.

References

1. Medical Masterclass contributors, Firth J. Haematology: multiple myeloma. Clin Med (Lond) 2019; 19: 58-60.
2. Kyle RA, Rajkumar SV. Multiple myeloma. Blood 2008; 111: 2962-72.
3. Ali SA, Khalifa HM, Bayoumi A, AlMazrooa S, Bin Madi NO, Akeel S, et al. Osteolytic lesion of the maxilla in an undiagnosed multiple myeloma patient identified incidentally by cone beam computed tomography. Am J Case Rep 2022; 23: e936585.
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021; 71: 209-49.
5. van de Donk NW, Pawlyn C, Yong KL. Multiple myeloma. Lancet 2021; 397: 410-27.
6. Neeravari A, Netravati P, Mohammed R, Ragupathi AR, Nagarajappa AH. Atypical imaging feature of non-secretory multiple myeloma. Ann Diagn Pathol 2011; 15: 268-72.
7. Charliński G, Jurczyszyn A. Non-secretory multiple myeloma: diagnosis and management. Adv Clin Exp Med 2022; 31: 95-100.
8. Dimopoulos MA, Kastritis E, Terpos E. Non-secretory myeloma: one, two, or more entities? Oncology (Williston Park) 2013; 27: 930-2.
9. Kamath P, Babu C, Tamgadge A, Pereira T. Multiple myeloma with presentation in the oral cavity. J Oral Maxillofac Pathol 2022; 26: 104-7.
10. Akyol R, Şirin Sarıbal G, Amuk M. Evaluation of mandibular bone changes in multiple myeloma patients on dental panoramic radiographs. Oral Radiol 2022; 38: 575-85.
11. Pontes FS, De Souza LL, Fonseca FP, Pontes HA. Mandibular lesion as the first sign of multiple myeloma in a young patient. J Oral Maxillofac Pathol 2019; 23(Suppl 1): 94-6.
12. Beaumont S, Koo RM, Harrison SJ. A Wolf in Sheep's clothing: a case report series of oral manifestations of multiple myeloma. Aust Dent J 2021; 66: 324-31.
13. Abed H, Burke M, Nizarali N. Oral and dental management for people with multiple myeloma: clinical guidance for dental care providers. Dent Update 2018; 45: 383-99.
14. Lee SB, Park CY, Lee HJ, Hong R, Kim WS, Park SG. Non-secretory multiple myeloma expressed as multiple extramedullary plasmacytoma with an endobronchial lesion mimicking metastatic cancer: a case report. World J Clin Cases 2022; 10: 7899-905.
15. Whicher JT, Davies JD, Grayburn JA. Intact and fragmented intracellular immunoglobulin in a case of non-secretory myeloma. J Clin Pathol 1975; 28: 54-9.
16. Gray ST, Antunovic DM, White AE. Non secretory multiple myeloma involving the maxilla: report of a case with update of biology and new approaches to management. Oral Oncol 1997; 33: 136-40.
17. Nutt SL, Hodgkin PD, Tarlinton DM, Corcoran LM. The generation of antibody-secreting plasma cells. Nat Rev Immunol 2015; 15: 160-71.
18. Cardoso RC, Gerngross PJ, Hofstede TM, Weber DM, Chambers MS. The multiple oral presentations of multiple myeloma. Support Care Cancer 2014; 22: 259-67.
19. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol 2020; 95: 548-67.
20. George ED, Sadovsky R. Multiple myeloma: recognition and management. Am Fam Physician 1999; 59: 1885-94.
21. Dupuis MM, Tuchman SA. Non-secretory multiple myeloma: from biology to clinical management. Onco Targets Ther 2016; 9: 7583-90.
22. Hemminki K, Försti A, Houlston R, Sud A. Epidemiology, genetics and treatment of multiple myeloma and precursor diseases. Int J Cancer 2021; 149: 1980-96.
23. Romano A, Marescalco MS, Liardo C, Villari L, Vetro C, Conticello C, et al. Oral lesion as unusual first manifestation of multiple myeloma: case reports and review of the literature. Case Rep Hematol 2014; 2014: 529452.
24. Almeida TM, Cavalcanti ÉF, Freitas AD, Magalhães RJ, Maiolino A, Torres SR. Can dentists detect multiple myeloma through oral manifestations? Rev Bras Hematol Hemoter 2018; 40: 43-9.
25. Moura LB, Gabrielli MF, Gabrielli MA, Filho VA. Pathologic mandibular fracture as first sign of multiple myeloma. J Craniofac Surg 2016; 27: e138-9.
26. Crowley M, Cronin O, Sleeman D, McKenna J. Multiple myeloma presenting as mandibular pain. J Ir Dent Assoc 2016; 62: 276-8.
27. Subitha K, Renu T, Lillykutty P, Letha V. Anaplastic myeloma presenting as mandibular swelling: diagnosis by cytology. J Cytol 2014; 31: 114-6.
28. Troeltzsch M, Oduncu F, Mayr D, Ehrenfeld M, Pautke C, Otto S. Root resorption caused by jaw infiltration of multiple myeloma: report of a case and literature review. J Endod 2014; 40: 1260-4.
29. Bottini GB, Steiner C, Melchardt T, Gaggl A. Multiple myeloma of the mandibular condyle: a rare presentation. Br J Oral Maxillofac Surg 2017; 55: 1046-7.
30. Goetze E, Walter C, Kämmerer PW. Osseous plasma cell neoplasm of the mandible for initial diagnosis of multiple myelo-

ma: case report and literature review. J Maxillofac Oral Surg 2015; 14 (Suppl 1): 469-74.
31. Piscatelli N, Hinchy N V, Frustino J, Reed LT, Zemer J, Alam N, et al. Oral soft tissue manifestation of multiple myeloma after kidney transplantation: a case report. Gen Dent 2022; 70: 37-40.
32. Zamagni E, Tacchetti P, Cavo M. Imaging in multiple myeloma: how? when? Blood 2019; 133: 644-51.
33. Rocha TG, Feitosa ÉF, Maiolino Â, de Magalhães Filho RJ, Guedes FR, Torres SR, et al. Imaginological characterization of multiple myeloma lesions of the jaws through cone-beam computed tomography. Oral Radiol 2020; 36: 168-76.
34. Gültekin SE, Büttner R. Clinical and pathomorphological aspects of odontogenic tumors. Pathologie (Heidelb) 2022; 43 (Suppl 1): 86-93.
35. ElKordy MA, ElBaradie TS, ElSebai HI, KhairAlla SM, Amin AA. Osteosarcoma of the jaw: challenges in the diagnosis and treatment. J Egypt Natl Canc Inst 2018; 30: 7-11.
36. Campolongo MG, Cabras M, Bava L, Arduino PG, Carbone M. Paget's disease of jaw bones as primary manifestation: a case report of a proper diagnosis made by general dentist. Gerodontology 2018; 35: 147-50.
37. Vega F, Chang CC, Medeiros LJ, Udden MM, Cho-Vega JH, Lau CC, et al. Plasmablastic lymphomas and plasmablastic plasma cell myelomas have nearly identical immunophenotypic profiles. Mod Pathol 2005; 18: 806-15.
38. Lae ME, Vencio EF, Inwards CY, Unni KK, Nascimento AG. Myeloma of the jaw bones: a clinicopathologic study of 33 cases. Head Neck 2003; 25: 373-81.
39. Abdelwahed Hussein MR. Non-Hodgkin's lymphoma of the oral cavity and maxillofacial region: a pathologist viewpoint. Expert Rev Hematol 2018; 11: 737-48.
40. Jiang AS, Wu Z, Wei EX, Ni H, You B, Yang T, et al. Plasma cell myeloma with dual expression of kappa and lambda light chains. Int J Clin Exp Pathol 2018; 11: 4718-23.