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Mandibular Plasmacytoma Relapse of Multiple Myeloma Masquerading as MRONJ: A Diagnostic Pitfall in Post-ASCT Surveillance: A Case Report

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ABSTRACT

Isolated plasmacytoma relapse of multiple myeloma (MM) is uncommon and portends a poor prognosis; mandibular involvement is exceptionally rare, and its clinical presentation in the post-autologous stem cell transplantation (ASCT) setting, particularly in patients with prior bisphosphonate exposure, can closely mimic medication-related osteonecrosis of the jaw (MRONJ), creating a critical diagnostic pitfall. A 62-year-old male with MM in sustained remission following ASCT and lenalidomide maintenance presented with a seven-month history of a non-healing extraction socket and progressive exophytic mandibular mass. Prior zoledronic acid therapy led to an initial diagnosis of MRONJ, delaying biopsy. Clinical examination revealed a 4×3 cm firm mass with lingual bone exposure; contrast-enhanced CT demonstrated osteolytic cortical destruction with inferior alveolar canal invasion and indeterminate incidental vertebral lytic foci. Incisional biopsy confirmed sheets of atypical plasma cells with eccentric nuclei and prominent mitotic activity, consistent with plasmacytoma. Comprehensive systemic workup, including bone marrow biopsy and serum protein electrophoresis, confirmed the absence of systemic MM relapse. The patient was treated with external beam radiotherapy (40 Gy in 20 fractions), achieving significant lesion regression. Focal residual bone exposure (<1 cm) attributed to combined bisphosphonate-radiation osteonecrosis was managed conservatively. The patient reported functional recovery and maintained acceptable quality of life at the three-month follow-up, with no evidence of local recurrence or systemic relapse. This case highlights that persistent oral lesions in MM patients must not be reflexively attributed to MRONJ without histopathological verification, especially when lesions fail to resolve following bisphosphonate cessation. Multidisciplinary surveillance at the oncology–dentistry interface is essential to avoid diagnostic delay in this vulnerable population.

Keywords: Multiple myeloma; Plasmacytoma; Mandibular neoplasms; Stem cell transplantation; Case report.

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Introduction

Multiple myeloma (MM) is a hematologic malignancy defined by the accumulation of clonal plasma cells within the bone marrow. It accounts for approximately 1% of all cancers and 10-15% of hematologic malignancies, with a higher incidence in males and a median age of diagnosis at 65 years. While the precise etiology remains elusive, established risk factors include exposure to environmental toxins, viral infections, radiation, obesity, and specific cytogenetic abnormalities implicated in disease pathogenesis [1-4]. Clinical manifestations—collectively termed CRAB criteria (hypercalcemia, renal insufficiency, anemia, and bone lesions)—encompass lytic bone lesions, pathological fractures, cytopenias, recurrent infections, and coagulopathies. The revised International Myeloma Working Group (IMWG) diagnostic criteria require ≥ 10% clonal plasma cells in bone marrow or biopsy-proven plasmacytoma, plus ≥ 1 myeloma-defining event: (i) CRAB features, (ii) clonal bone marrow plasma cells ≥ 60%, (iii) serum free light-chain ratio ≥ 100 (provided involved FLC level is ≥ 100 mg/L), or (iv) > 1 focal lesion on MRI ≥ 5 mm in size [5,6]. Early detection through integrated laboratory, cytogenetic, and radiographic assessment is crucial for enhancing survival.

Contemporary management combines traditional modalities (chemotherapy, radiotherapy) with novel agents: proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies. Autologous stem cell transplantation (ASCT) remains the standard of care for transplant-eligible patients, with recent studies demonstrating improved survival outcomes despite the advent of novel immunotherapies [7]. High-dose chemotherapy with ASCT and PI/IMiD-based regimens achieves remission in approximately 30% of patients, with median survival increasing by 8-10 years in the era of new drugs [7,8]. Plasmacytoma, a rare plasma cell dyscrasia, presents as solitary or multifocal tumors in bone (solitary plasmacytoma of bone, SPB) or soft tissue (extramedullary plasmacytoma, EMP), lacking systemic myeloma features. The WHO classifies SPB into:

1. SPB with minimal marrow involvement (< 10% clonal plasma cells; 20-60% progression to MM within 3 years).

2. SPB without marrow involvement (~20% progression risk).

Multiple solitary plasmacytomas (multifocal lesions without marrow involvement) are exceptionally rare. [9-12]. Treatment involves localized radiotherapy ± surgery/systemic therapy. Extramedullary disease (EMD) in MM, including localized plasmacytoma relapse, represents a distinct clinical entity associated with poor prognosis and aggressive behavior. Current data indicate EMD frequencies of 7-17% at diagnosis and 6-20% at relapse [12,13]. The formation of EMD originates from the "bone marrow escape" of plasma cell subclones, which detach from dependency on the bone marrow microenvironment and infiltrate soft tissues. This case highlights the importance of considering plasmacytoma in patients with plasma cell dyscrasia presenting with persistent mandibular lesions post-ASCT.

Patient Information

A 62-year-old male presented to the Department of Oral and Maxillofacial Medicine at Isfahan Dental School in December 2023, reporting persistent left mandibular paresthesia and an enlarging exophytic mass in the region of the extracted first and second molars. The patient's medical history revealed a diagnosis of multiple myeloma (MM) in October 2020 following evaluation for lower back pain, chest discomfort, and fatigue.

Primary Concerns: Progressive mandibular swelling, paresthesia, and non-healing extraction sockets persisting for seven months.

Medical History: Multiple myeloma diagnosed in October 2020; no family history of hematologic malignancies; non-smoker; no known allergies.

Previous Interventions: Initial bortezomib, dexamethasone, and lenalidomide (VRD) therapy (four cycles), ASCT, lenalidomide maintenance, and bisphosphonate therapy (zoledronic acid) until May 2023.

Clinical Findings

Initial therapy comprised four cycles of bortezomib, dexamethasone, and lenalidomide (VRD) with monthly zoledronic acid. After a partial response, he underwent autologous stem cell transplantation (ASCT), followed by lenalidomide maintenance and quarterly zoledronic acid. Clinical remission was sustained until May 2023, when he developed localized mandibular pain. Subsequent dental extraction of teeth #36 and #37 resulted in non-healing sockets and persistent pain. His oncologist initially suspected medication-related osteonecrosis of the jaw (MRONJ), prompting discontinuation of zoledronic acid. Despite this, an exophytic mass emerged at

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the extraction site, progressively enlarging over seven months (Figure 1).

Clinical and Radiographic Findings

Examination identified a 4 × 3 cm firm, smooth-surfaced, non-ulcerated mass involving the left posterior mandibular ridge, extending buccolingually with lingual bone exposure. The mass was non-tender on palpation with no regional lymphadenopathy. Intraoral examination revealed mild trismus and altered sensation in the left mandibular nerve distribution. Panoramic radiography demonstrated a poorly demarcated osteolytic lesion with a "moth-eaten" pattern, encroaching on the inferior alveolar canal (Figure 2). Contrast-enhanced maxillofacial CT confirmed cortical destruction of the left mandible and revealed incidental lytic foci in cervical vertebrae (Figure 3).

Diagnostic Assessment

Primary differential diagnoses included:

1. Mandibular plasmacytoma (localized plasmacytoma relapse of MM).

2. Non-Hodgkin lymphoma with mandibular involvement.

3. Medication-related osteonecrosis of the jaw (MRONJ).

4. Odontogenic cyst or tumor.

5. Osteosarcoma or other primary bone malignancy.

Diagnostic Methods

Laboratory Testing: Complete blood count, comprehensive metabolic panel, serum protein electrophoresis, immunofixation, serum free light chains, and bone marrow aspiration with cytogenetics.

Imaging: Panoramic radiography, contrast-enhanced CT of the maxillofacial region, and whole-body imaging to exclude systemic disease according to current IMWG guidelines [3].

Histopathology: Incisional biopsy of the mandibular mass revealed sheets of atypical plasmacytoid cells (Figure 4):

- Eccentrically positioned nuclei with prominent nucleoli.
- Cytoplasmic hyperchromasia and pleomorphism.
- Frequent mitotic figures.

Final Diagnosis: Isolated mandibular plasmacytoma representing localized MM relapse post-ASCT (plasmacytoma relapse without evidence of systemic myeloma progression).

Prognostic Characteristics: Localized disease without systemic involvement; good performance status; no high-risk cytogenetic features identified.

Therapeutic Intervention

The patient received localized external beam radiotherapy as the primary treatment modality:

- Dose: 40 Gy delivered in 20 fractions over 4 weeks.
- Technique: 3D conformal radiotherapy with appropriate margins.
- Rationale: Standard of care for localized plasmacytoma; surgery avoided due to prior bisphosphonate exposure and MRONJ risk.

Recent studies demonstrate that radiotherapy (40-50 Gy) achieves local control rates greater than 80% for solitary plasmacytomas, making it the cornerstone of treatment [8,14]. No modifications to the radiotherapy regimen were required. Systemic therapy was not initiated, given the localized nature of the disease and absence of systemic MM relapse.

Follow-up and Outcomes

Post-treatment imaging showed significant lesion regression with marked reduction in the soft tissue mass and stabilization of the osteolytic lesion. However, a small area (< 1 cm) of lingual bone exposure persisted, attributed to the combined effects of prior bisphosphonate therapy and radiation. This finding aligns with recent research demonstrating increased MRONJ risk in patients receiving combined bisphosphonate and radiation therapy, with incidence rates of up to 11% in high-dose cancer patients [15]. Given the minimal bone exposure and absence of symptoms, management transitioned to supportive care using daily 2% hydrogen peroxide rinses with prophylactic antibiotics as needed and regular dental follow-up for oral hygiene maintenance. Current evidence supports conservative management for limited MRONJ (< 1 cm exposed bone) with supportive care and antimicrobial therapy [15]. Treatment was well-tolerated with no acute radiation toxicity. Patient maintained adequate nutritional status throughout treatment. At the three-month follow-up in May 2024, there was no sign of local recurrence. The bone exposure remained stable, and there were no indications of infection. The patient continued

to maintain remission from systemic multiple myeloma and had good functional status and quality of life. (Figure 5).

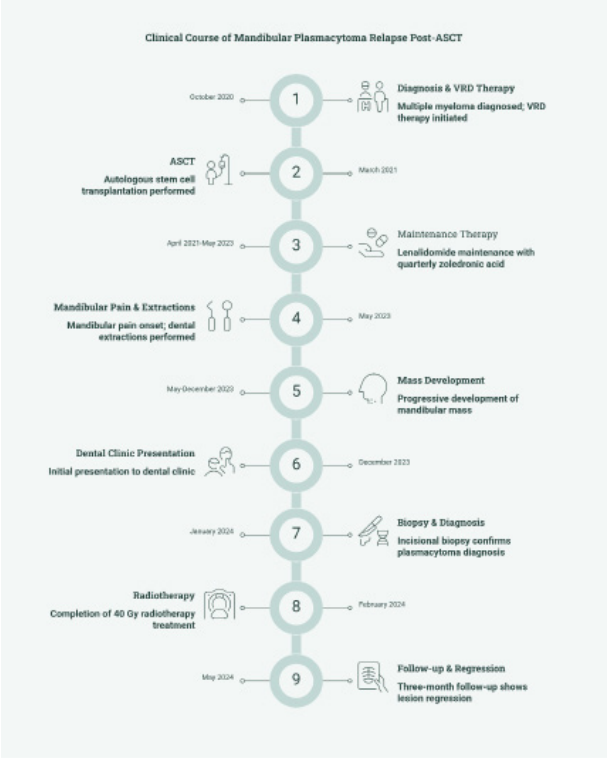


Figure 1. A-B: Clinical presentation showing a 4 × 3 cm exophytic mass in the left posterior mandibular region with a smooth, non-ulcerated surface and associated lingual bone exposure following dental extractions.

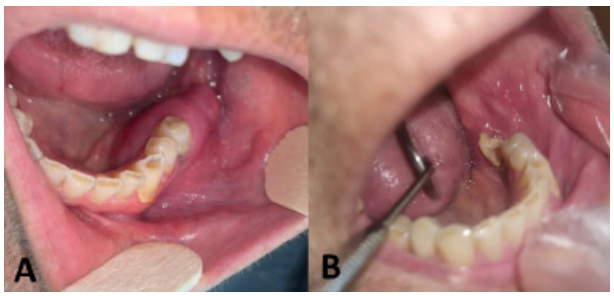


Figure 2. Panoramic radiograph demonstrating a poorly demarcated osteolytic lesion with a characteristic "moth-eaten" pattern in the left mandibular body, extending toward the inferior alveolar canal.



Figure 3. Contrast-enhanced CT scan showing cortical destruction of the left mandible with associated soft tissue mass and involvement of the mandibular canal.



Figure 4. Histopathological examination (H&E staining, 400x magnification) revealing sheets of atypical plasma cells with eccentric nuclei, prominent nucleoli, and increased mitotic activity characteristic of plasmacytoma.

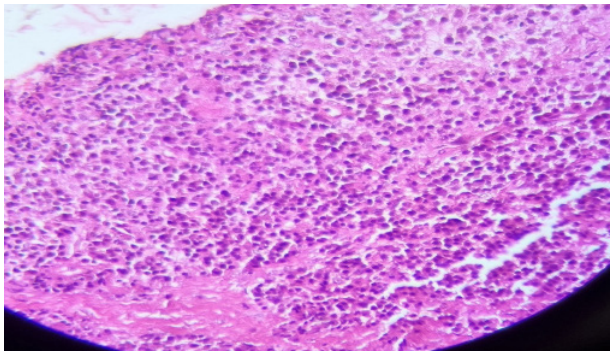


Figure 5. Timeline of clinical course of mandibular plasmacytoma relapse of the patient after autologous stem cell transplantation.

Discussion

Recent advancements in the treatment of multiple myeloma have significantly improved patient outcomes. Autologous stem cell transplantation (ASCT) after high-dose chemotherapy remains a cornerstone therapy that enhances survival and is the current standard treatment for eligible newly diagnosed multiple myeloma (NDMM) patients. In the era of novel drugs, early ASCT still results in longer progression-free survival (PFS), with median survival increasing by 8-10 years [16]. However, challenges like disease relapse remain, with extramedullary relapse representing a particularly aggressive form. The significance of this case lies not in the rarity of mandibular bone involvement per se, but in the near-perfect clinical mimicry of MRONJ that delayed histopathological evaluation for seven months. Unlike the majority of reported post-ASCT plasmacytoma relapses—which manifest at paravertebral, rib, or skull sites detectable through routine systemic surveillance—mandibular relapse presents at the interface of dentistry and oncology, a clinical boundary where

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neither specialty has clear ownership of follow-up responsibility. This case exposes a structural surveillance gap: patients with MM on bisphosphonate therapy who undergo dental procedures are managed by oral surgeons and dentists who may not reflexively consider neoplastic relapse in the differential of a non-healing socket, particularly when systemic biomarkers remain negative.

Epidemiology and Clinical Significance

Extramedullary disease (EMD) in MM represents a distinct clinical entity with current data indicating EMD frequencies of 7-17% at diagnosis and 6-20% at relapse [17]. Plasmacytoma relapse post-ASCT is infrequent, representing only 14% of recurrences in large cohorts. While insidious and classic biochemical relapses dominate, extramedullary presentations correlate strongly with initial plasmacytoma history and portend a poorer prognosis. Mandibular involvement is exceptionally rare, accounting for only 4.4% of solitary plasmacytomas. Recent case series have documented only 89 cases of mandibular plasmacytoma in the English literature, with limited cases reporting MM relapse in this location [9,10,18]. Its nonspecific clinical-radiographic features—often mimicking benign cysts, odontogenic tumors (e.g., keratocyst, ameloblastoma), or malignancies (e.g., osteosarcoma, lymphoma)—frequently delay diagnosis. Consistent with epidemiological data, our 62-year-old male patient presented with posterior mandibular pain, swelling, and paresthesia—classic symptoms also encompassing tooth mobility and pathological fractures.

Diagnostic Considerations

Radiographically, mandibular plasmacytomas exhibit variable lytic patterns, including unilocular or multilocular radiolucencies or destructive "moth-eaten" lesions. Our case demonstrated the latter, with cortical perforation and inferior alveolar canal invasion. Incidentally noted lytic foci in the cervical vertebrae on CT were reviewed in conjunction with whole-body imaging; they showed no progression and were not considered myeloma-defining, supporting the isolated nature of the relapse. Recent guidelines emphasize the importance of advanced imaging modalities, including PET-CT and whole-body MRI, for comprehensive assessment of extramedullary disease [3]. Histopathology typically reveals sheets of atypical plasma cells with eccentric nuclei, "clock-face" chromatin, and mitotic activity. Although immunohistochemical confirmation of clonality (CD138 with kappa/lambda light-chain restriction) is recommended for the definitive diagnosis of solitary plasmacytoma, it could not be performed in this case, as the biopsy material was exhausted during routine processing and no further tissue could be obtained; the diagnosis therefore rests on morphology in the context of the patient's known multiple myeloma, negative systemic staging, and the complete radiotherapy response (see Limitations). The diagnosis of solitary plasmacytoma requires absence of systemic MM criteria according to updated IMWG guidelines (hypercalcemia, renal dysfunction, anemia, > 10% clonal cells, or multifocal skeletal lesions) [6,14,19,20].

Treatment Approach and Outcomes

Radiotherapy (40-50 Gy) remains the cornerstone of solitary plasmacytoma management, achieving local control rates greater than 80%. Recent evidence suggests that targeted therapies are now indicated in solitary plasmacytomas of the jaw, with the optimal approach (radiotherapy, chemotherapy, and surgery) depending on tumor size, invasion, metastasis, and patient condition [14,21,22]. Surgery is reserved for functionally non-critical sites. In this case, the patient underwent radiation therapy, receiving a cumulative dose of 40 Gy across 20 sessions. Given the patient's history of bisphosphonate therapy and the risk of developing medication-related osteonecrosis of the jaw (MRONJ), radical surgical intervention was considered inappropriate. Recent studies demonstrate significantly higher MRONJ risk in patients receiving denosumab compared to bisphosphonates, with hazard ratios of 5.03 for low-dose and 5.07 for high-dose recipients [15]. Post-radiotherapy assessment revealed lesion regression; however, a focal area of necrotic bone was identified. This finding was anticipated, considering the radiation administered to the mandibular region and the patient's previous intravenous bisphosphonate treatment. Contemporary evidence indicates that bisphosphonate-related osteonecrosis develops more slowly than denosumab-related cases, with with bisphosphonates being retained in the skeleton for up to 10 years, compared with denosumab's plasma half-life of approximately 26 days. [15]. The extent of the necrotic area was limited, requiring only supportive care, including antibiotics and hydrogen peroxide mouthwash.

Surveillance and Monitoring Considerations

Current MM surveillance protocols emphasize the importance of minimal residual disease (MRD) assessment using next-generation sequencing, flow cytometry, and advanced imaging. Recent guidelines recommend that both PET-CT and whole-body diffu-

sion-weighted MRI are complementary to bone marrow MRD for comprehensive evaluation [21]. MRD negativity serves as a surrogate marker for treatment efficacy and survival prediction, with bone marrow MRD negativity defined as the absence of malignant plasma cells within 100,000 nucleated bone marrow cells (sensitivity threshold < 10^{-5}). Furthermore, it is noteworthy that our literature review did not uncover any documented instances of multiple myeloma relapse presenting as mandibular plasmacytoma, adding a unique dimension to this case. In a comprehensive study involving 1,304 multiple myeloma patients from 1970 to 2018, 967 experienced treatment relapse, with 192 cases identified as plasmacytoma. Among these, 14.6% had paraskeletal plasmacytoma and 5.1% had extramedullary plasmacytoma. The most frequently affected paraskeletal sites included the paravertebral vertebrae, rib cage, skull, pelvis, and long bones, with no reported cases involving the jawbone.

Clinical Implications and Future Directions

This case emphasizes several critical clinical considerations:

1. Enhanced Surveillance: Current MM surveillance protocols may need refinement to detect localized relapses, particularly in anatomical sites with prior invasive procedures.

2. Multidisciplinary Approach: Collaboration between dental, oncology, and pathology specialists is essential for optimal patient care.

3. Risk-Benefit Assessment: Prior bisphosphonate exposure significantly influences treatment decisions, requiring careful consideration of MRONJ risk.

4. Novel Therapeutic Considerations: Emerging immunotherapies, including bispecific antibodies and CAR-T cell therapy, may offer future treatment options for extramedullary relapse.

Recent advances in MRD monitoring using mass spectrometry in peripheral blood offer promise as less invasive alternatives to bone marrow assessment, with studies demonstrating that patients achieving both bone marrow (NGS) and blood (LC-MS) negativity show 89% progression-free survival at 5 years [19,23,24].

Limitations

This report has several limitations. First, immunohistochemical confirmation of monoclonal plasma-cell differentiation (e.g., CD138, CD38, IRF4/MUM1, and kappa/lambda light-chain restriction)—recommended in current expert criteria for solitary plasmacytoma—was not performed. The diagnosis was established on morphological grounds, supported by the patient's documented history of multiple myeloma, a comprehensive negative systemic workup, and the complete local response to radiotherapy. No archival tissue is available for retrospective staining, as the incisional biopsy material was exhausted during routine processing and no surgical specimen was obtained, radiotherapy having been deliberately selected over resection. Re-biopsy solely for immunohistochemistry was considered unjustifiable in this post-ASCT, immunocompromised patient with prior zoledronic acid exposure, given the risk of osteonecrosis and impaired wound healing at the irradiated mandible, and the absence of any anticipated change in management.

Consequently, clonality was not confirmed immunophenotypically, and CD138-positive mimics—most notably plasmablastic lymphoma—cannot be formally excluded on morphology alone; however, the patient's age, absence of immunodeficiency, known plasma-cell myeloma history, and indolent radiosensitive disease course render these alternative diagnoses highly unlikely. This case nonetheless illustrates that where tissue is limited, clinicopathological correlation and follow-up response to therapy may serve as pragmatic, though imperfect, surrogates for immunophenotypic confirmation.

Conclusion

This case demonstrates that isolated mandibular plasmacytoma relapse can present as a non-healing oral lesion clinically and radiographically indistinguishable from MRONJ in patients with MM receiving bisphosphonate therapy post-ASCT. Three clinically actionable lessons emerge: **(1)** persistent oral lesions in MM patients should prompt expedited histopathological biopsy regardless of MRONJ suspicion, particularly when the lesion fails to regress following bisphosphonate cessation; **(2)** treatment planning in this setting must account for combined bisphosphonate-radiation osteonecrosis risk, with conservative surgical avoidance where feasible; and **(3)** multidisciplinary review involving both oncology and oral medicine is essential at any stage of mandibular workup in MM patients. Longer follow-up data and standardized surveillance guidelines at the dentistry–oncology interface are needed to define optimal management pathways for this rare relapse site.

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Conflict of Interest

There is no conflict of interest to declare.

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