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BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE MAXILLARY: CASE REPORT

|Basma ZAHER [1]* | Soukaina OUJDAD [1] | and | Lamia KISSI [1]|

[1.] Hassan II university | dental medicine faculty of Casablanca | department of oral medicine and oral surgery | Morocco |

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ABSTRACT

Background: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a severe iatrogenic complication of antiresorptive therapy, most frequently observed in oncological patients receiving high-dose intravenous bisphosphonates. Despite growing clinical recognition since its first description in 2003, the condition remains difficult to manage, with no universally accepted therapeutic standard and a pathophysiology that is still incompletely understood. **Case presentation:** We report the case of a 29-year-old woman with acute myeloid leukemia, treated with intensive chemotherapy and intravenous bisphosphonates for four months, who presented with recurrent upper genian cellulitis, bone denudation, and loss of her maxillary dental bridge. Intraoral examination revealed extensive exposed necrotic bone extending from tooth 13 to tooth 26, with marked mucosal inflammation, purulent deposits, and spontaneous loss of teeth 11, 12, 21, and 25. Panoramic radiography demonstrated empty alveolar sockets with absence of bone healing, and cone-beam computed tomography (CBCT) confirmed complete sequestration of the dentoalveolar block 13–25, with a radiolucent line located 3 to 5 mm from residual apices. Clinical staging was consistent with Stage III BRONJ according to the 2022 American Association of Oral and Maxillofacial Surgeons (AAOMS) criteria. Initial management consisted of antiseptic irrigations, antibiotic therapy, and analgesics. The patient died three weeks after the consultation. **Interpretation:** This case illustrates the fulminant potential of BRONJ in young immunocompromised oncological patients, where the combination of high-potency intravenous bisphosphonates and chemotherapy-induced immunosuppression dramatically accelerates disease onset and progression. CBCT proved essential for precise three-dimensional delineation of the sequestrated bone block, beyond what panoramic radiography could provide. This observation reinforces the absolute necessity of systematic pre-therapeutic oral assessment and elimination of infectious dental foci prior to initiating any intravenous antiresorptive regimen, alongside close interdisciplinary collaboration between oncologists, hematologists, oral surgeons, and dental practitioners. For this severe and potentially life-threatening complication, prevention remains immeasurably more effective than cure..

1. INTRODUCTION

Bisphosphonates (BPs) constitute a major class of antiresorptive agents that exert their pharmacological action primarily through the inhibition of osteoclast-mediated bone resorption. By binding with high affinity to hydroxyapatite crystals at sites of active bone remodeling, these compounds suppress osteoclastogenesis, promote osteoclast apoptosis, and profoundly reduce bone turnover (AlRowis et al., 2022; Kawahara et al., 2021). Their clinical indications are broad, encompassing the management of osteoporosis, Paget's disease of bone, hypercalcemia of malignancy, and the prevention of skeletal-related events (SREs) in patients with bone metastases from solid tumours, including breast, prostate, and lung carcinomas, as well as in multiple myeloma (AlRowis et al., 2022; Ruggiero et al., 2022). Two main categories exist: oral bisphosphonates, primarily prescribed for benign metabolic bone conditions, and intravenous formulations, notably zoledronic acid (zoledronate) and pamidronate, characterized by substantially higher potency and bioavailability, and predominantly indicated in oncological settings (Kawahara et al., 2021).

The widespread clinical use of BPs has, however, been shadowed by a severe and increasingly recognized adverse effect: osteonecrosis of the jaw (ONJ). This condition was first described in the scientific literature in 2003, when Marx reported 36 patients presenting with painful exposed bone of the mandible or maxilla, all receiving pamidronate or zoledronic acid (Marx, 2003). This initial report prompted an exponential growth in clinical observation and research, rapidly establishing bisphosphonate-related osteonecrosis of the jaw (BRONJ) as a distinct and serious iatrogenic entity. In 2014, acknowledging the expanding spectrum of implicated molecules, particularly the RANKL inhibitor denosumab and antiangiogenic agents, the American Association of Oral and Maxillofacial Surgeons (AAOMS) recommended adoption of the broader term medication-related osteonecrosis of the jaw (MRONJ), a nomenclature reaffirmed and

refined in the 2022 AAOMS position paper update (Ruggiero et al., 2022). The diagnostic triad of MRONJ, as defined by the AAOMS, requires: (a) current or previous treatment with antiresorptive or antiangiogenic agents; (b) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than eight weeks; and (c) no history of radiation therapy to the jaws or metastatic disease to the jaws (Ruggiero et al., 2022). Clinically, the presentation spans a wide spectrum, from asymptomatic bone exposure to severe infectious complications, pathological fracture, and orocutaneous fistula formation, with significant impact on patients' quality of life (AlRowis et al., 2022; Kawahara et al., 2021). From an epidemiological standpoint, the incidence of MRONJ varies considerably according to the route of administration, the cumulative dose, and the underlying indication. Among patients with malignant disease treated with bisphosphonates and denosumab, the incidence of MRONJ reaches up to 15%, in sharp contrast to rates as low as 0.01% in patients with osteoporosis on oral regimens. Intravenous nitrogen-containing bisphosphonates, and zoledronic acid in particular, carry the highest risk, especially when administered at the high doses and frequencies used in oncological settings (Kawahara et al., 2021). The risk is further compounded by local and systemic factors: invasive dental procedures (notably tooth extraction), pre-existing periodontal or periapical infection, corticosteroid and immunosuppressive co-therapy, advanced age, and comorbidities such as diabetes mellitus and tobacco use (AlRowis et al., 2022; Ruggiero et al., 2022).

The pathophysiology of BRONJ/MRONJ remains incompletely elucidated. Several non-mutually exclusive mechanisms have been proposed, including: (i) profound suppression of jawbone turnover, rendering the mandible and maxilla, which exhibit the highest bone remodeling rates in the skeleton, particularly vulnerable; (ii) inhibition of angiogenesis, notably with zoledronate, impairing vascular supply to areas of micro-injury; (iii) local infection and dysbiosis, with superinfection by Actinomyces species frequently documented in biopsies of necrotic bone; and (iv) direct soft tissue toxicity with compromised mucosal healing (AlRowis et al., 2022; Kawahara et al., 2021; Ruggiero et al., 2022). The exclusive predilection of this osteonecrosis for the jawbones, in contrast to other skeletal sites exposed to equivalent pharmacological concentrations, remains the subject of ongoing investigation and debate. Clinically, the maxilla is affected less frequently than the mandible, accounting for approximately 20 to 30% of BRONJ cases, but maxillary involvement tends to carry a more severe prognosis due to anatomical proximity to the maxillary sinuses, the nasal floor, and orbital structures (Kawahara et al., 2021; AlRowis et al., 2022). Cases occurring in oncological patients receiving intravenous bisphosphonates typically present at more advanced stages, with more extensive necrosis, greater infectious morbidity, and a more refractory clinical course than those arising in patients on oral therapy for osteoporosis (Ruggiero et al., 2022).

Herein we report the case of a 29-year-old woman with acute myeloid leukemia, treated with intensive chemotherapy and intravenous bisphosphonates, who developed severe bisphosphonate-related osteonecrosis of the maxilla with complete sequestration of the dentoalveolar block extending from tooth 13 to tooth 25. This case illustrates the devastating potential of BRONJ in young oncological patients and underscores the critical importance of systematic oral assessment and interdisciplinary surveillance prior to and during antiresorptive therapy in this high-risk population.

2. Clinical case

A 29-year-old woman reported recurrent upper genian cellulitis with bone denudation and the loss of her maxillary dental bridge. Her medical history showed that she was being treated in oncology for acute myeloid leukemia with intensive chemotherapy and intravenous bisphosphonates for the last 4 months. The patient reported that the problem began 3 months ago with purplish, bleeding mucositis in the upper incisor-canine region. The mucositis then spread to adjacent teeth, resulting in the loss of the bridge from teeth 13 to 24 and three successive episodes of cellulitis despite antibiotic treatment with the spontaneous loss of teeth 11, 12, 21 and 25 [Figure 1].

Figure 1: pictures taken previously by the patient. (a) An extra-oral photographs of the patient, having swelling on upper right side of the face. (a,b) An intraoral photograph showing purplish, bleeding mucositis.

Intraoral clinical photographs (frontal view, Fig. 2a; occlusal view, Fig. 2b) demonstrating extensive exposed necrotic bone involving the maxillary anterior and premolar region, extending from tooth 13 to tooth 26. The necrotic bone

appears yellowish-white, devitalized, and partially covered with greenish-brown purulent deposits, consistent with secondary bacterial superinfection. The surrounding soft tissues exhibit marked erythema, mucosal inflammation, and ulceration along the necrotic bone margins. Residual dental roots are visible within the necrotic field, with evidence of severe periodontal attachment loss. The overall clinical presentation is consistent with Stage III bisphosphonate-related osteonecrosis of the jaw (BRONJ), as defined by the AAOMS 2022 criteria, characterized by exposed and infected necrotic bone with extension beyond the alveolar region [Figure 2].

Figure 2: (a,b) intraoral photograph showing exposed, necrotic bone extended from the 13th to the 26th tooth.

The panoramic radiograph (orthopantomogram) demonstrating empty alveolar sockets at the sites of teeth 11, 12, 21, and 25, with no evidence of normal bone healing or alveolar ridge remodeling [Figure 3]. A poorly defined periapical radiolucent lesion is observed extending along the alveolar block 12–25, suggestive of ongoing bone sequestration. The absence of a normal trabecular bone pattern within this region, combined with the lack of cortical definition at the alveolar crest, is consistent with advanced bisphosphonate-related osteonecrosis of the maxilla.

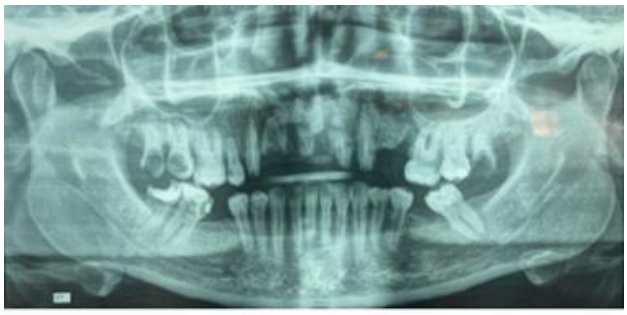

Figure 3: Panoramic dental X-ray shows the absence of teeth 11, 12, 21, and 25, with the presence of a radiolucent lyse apically of the alveolar block 12-25.

Perpendicular-oblique, frontal sections and 3D reconstruction of the CBCT showed the presence of a clearly visible radiolucent line located 3 to 5 mm from the apices of the remaining teeth highlighting the complete sequestration of the dentoalveolar block 13-25 [Figure 4].

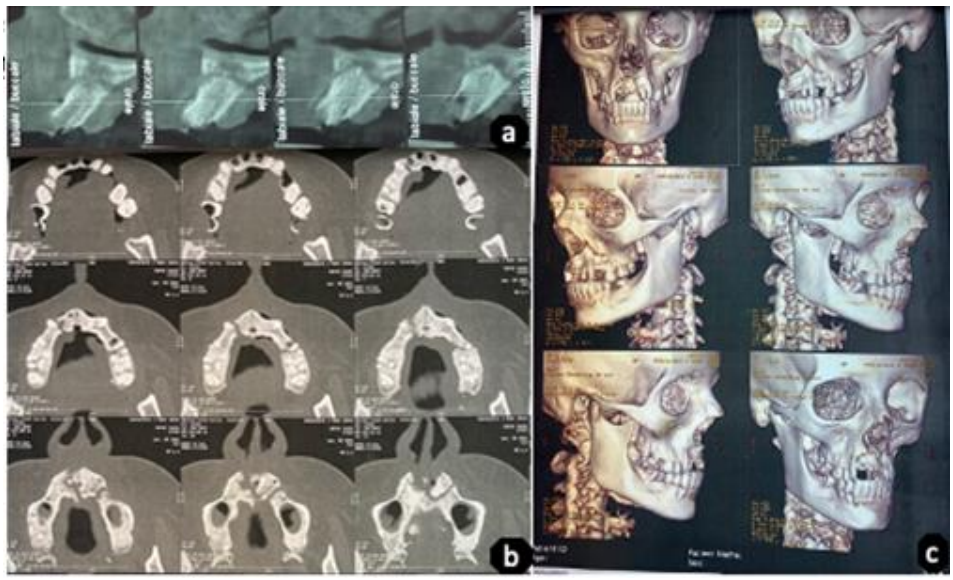

Figure 4: (**a**) Perpendicular-oblique view, (**b**) frontal view, and (**c**) 3D reconstruction of computed tomography shows a complete sequestration of the dentoalveolar block 13–25.

The patient was initially treated with anti-inflammatory irrigations and a prescription for antibiotics and analgesics. There was no further follow-up care as, Unfortunately, the patient passed away three weeks after our visit.

3. DISCUSSION

Associated Medications and Pharmacological Profile of Bisphosphonates

Bisphosphonates (BPs) represent the primary therapeutic class implicated in the development of medication-related osteonecrosis of the jaw (MRONJ/BRONJ). These antiresorptive agents exert their pharmacological action by inhibiting osteoclast differentiation and function, promoting osteoclast apoptosis, and substantially reducing bone turnover (AlRowis et al., 2022; Kawahara et al., 2021). Their clinical indications span a broad spectrum, ranging from benign metabolic bone conditions, primarily osteoporosis and Paget's disease of bone, to the management of skeletal-related events in oncological settings, including bone metastases from solid tumors and osteolytic lesions associated with multiple myeloma (Ruggiero et al., 2022; Sacco et al., 2021).

Two routes of administration are distinguished, each carrying a distinct risk profile. Oral bisphosphonates, including alendronate and risedronate, are primarily prescribed for benign conditions and are associated with a considerably lower incidence of BRONJ. Intravenous bisphosphonates, notably zoledronic acid and pamidronate, are reserved for oncological indications, exhibit substantially greater pharmacological potency, and accumulate in bone over a prolonged half-life exceeding ten years (AlRowis et al., 2022; Ruggiero et al., 2022). In a large case-control study of bisphosphonate-treated patients with metastatic cancer, Van Poznak et al. (2022) confirmed that patients receiving zoledronic acid presented a significantly higher risk of developing osteonecrosis of the jaw than those receiving pamidronate, with an odds ratio of 0.18 favoring pamidronate. In the reported case, the patient was receiving intravenous bisphosphonates in the context of acute myeloid leukemia, placing her in the highest-risk category from the outset. Antiangiogenic targeted therapies may also contribute to the pathogenesis of osteonecrosis through their inhibitory effect on neovascularization, thereby exacerbating disease progression by reducing blood supply to necrotic bone areas (Sharma et al., 2023; Sacco et al., 2021).

Clinical Manifestations

The clinical presentation of BRONJ/MRONJ encompasses a wide spectrum, ranging from asymptomatic bone exposure, reported in up to 94% of cases, to severe forms including intense pain, soft tissue swelling, recurrent infections, trigeminal nerve paresthesia, tooth loss, intra- and extraoral fistula formation, oroantral communications, and pathological jaw fractures (Sharma et al., 2023; AlRowis et al., 2022). These complications substantially impair patients' quality of life, compromising mastication, phonation, and oral hygiene (Kawahara et al., 2021). The present case is clinically remarkable in several respects: the patient was 29 years old, an unusually young age for BRONJ, as most published series report a mean age exceeding 60 years (AlRowis et al., 2022; McGowan et al., 2018), and presented with extensive maxillary necrosis extending from tooth 13 to tooth 26, with three successive episodes of cellulitis and the spontaneous loss of four teeth within three months. This fulminant clinical course is attributable to the severe immunosuppression concomitantly induced by intensive chemotherapy, a recognized aggravating factor in the development and progression of MRONJ (Sacco et al., 2021).

Diagnostic Criteria

The diagnosis of BRONJ rests on three criteria defined by the AAOMS: (a) current or previous treatment with antiresorptive or antiangiogenic agents; (b) exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region persisting for more than eight weeks; and (c) no history of radiation therapy to the jaws or metastatic disease to the jaws (Ruggiero et al., 2022). All three criteria were met in the present case. Radiological assessment by panoramic radiography and CBCT is essential to precisely delineate the extent of necrotic lesions. In this case, CBCT demonstrated a clearly visible radiolucent line located 3 to 5 mm from the apices of the remaining teeth, highlighting complete sequestration of the dentoalveolar block 13 to 25, information that panoramic radiography alone could not provide. Histopathological examination, following removal of bone sequestra, confirms the necrotic nature of the exposed bone and rules out bone metastasis, constituting an indispensable diagnostic complement in oncological presentations (Sharma et al., 2023; Kawahara et al., 2021).

Pathophysiology

The pathophysiology of bisphosphonate-induced osteonecrosis remains incompletely elucidated. Several non-mutually exclusive hypotheses have been proposed to account for its exclusive anatomical predilection for the jaw bones, despite systemic pharmacological exposure. First, profound suppression of bone remodeling: bisphosphonates block the remodeling cycle by inhibiting osteoclast differentiation and function and by increasing osteoclast apoptosis. Since bone turnover in the mandible and maxilla is approximately ten times higher than in other skeletal segments, owing to repeated microtrauma from mastication, pharmacological blockade of this cycle generates disproportionate osseous

complications at these sites (Sharma et al., 2023; Kawahara et al., 2021). Second, inflammation and infection: dental surgical trauma, particularly tooth extraction, constitutes the primary triggering factor for BRONJ, inducing local inflammation to which bisphosphonate-exposed jaws cannot respond through normal bone remodeling. Chronic dental infections, periodontal and periapical, are frequently implicated, with Actinomyces superinfections regularly documented in necrotic bone biopsies (AlRowis et al., 2022; McGowan et al., 2018). Third, reduction of angiogenesis: inhibition of angiogenesis induced by antiangiogenic agents as well as by certain bisphosphonates such as zoledronic acid exacerbates osteonecrosis progression by reducing vascular supply to injured areas (Sharma et al., 2023; Ruggiero et al., 2022). Fourth, immunosuppression: the existence of systemic immunosuppression, whether disease-induced or iatrogenic, has been proposed as a significant cofactor in MRONJ development. A systematic review by Sacco et al. (2021) specifically analyzed outcomes of MRONJ in non-oncological immunosuppressed patients and confirmed that invasive dental procedures were the most common triggers of MRONJ in this population, with a high frequency of postoperative complications and recurrence.

Risk Factors

In cancer patients, BRONJ may arise spontaneously or be precipitated by oral surgical procedures. High-dose intravenous bisphosphonates and prolonged duration of exposure constitute the primary determinants of risk (AlRowis et al., 2022; Van Poznak et al., 2022). A systematic review by McGowan et al. (2018) identified the following as significant risk factors for MRONJ: intravenous bisphosphonate administration, oncological indication, tooth extraction, corticosteroid use, diabetes mellitus, and pre-existing periodontal or periapical disease. In the present case, although treatment had been administered for only four months prior to symptom onset, the intensity of the oncological protocol combining intensive chemotherapy with intravenous bisphosphonates, and the associated severe immunosuppression, account for the rapidity and severity of the clinical course. A case-control study by McGowan et al. (2019) further demonstrated that systemic comorbidities, quantified as a comorbidity-polypharmacy score, were significantly associated with MRONJ development, reinforcing the multifactorial nature of this condition. Additional risk factors identified in the literature include corticosteroid and immunosuppressive co-therapy, diabetes mellitus, tobacco use, alcohol consumption, poor oral hygiene, jaw exostoses and bony prominences, and the thinness of the overlying gingival mucosa (AlRowis et al., 2022; Ruggiero et al., 2022; McGowan et al., 2018).

Treatment and Prevention

Management of established BRONJ must be conducted in a hospital setting, within a multidisciplinary framework involving oncologists, hematologists, oral and maxillofacial surgeons, and dental practitioners (Ruggiero et al., 2022). Treatment is guided by clinical staging according to the AAOMS classification. At Stage I, exposed bone without infection in an asymptomatic patient, conservative management combining antiseptic irrigations and antibiotic therapy is recommended. At Stage II, exposed bone with infection in a symptomatic patient, a limited surgical revision of the affected area may be considered alongside medical therapy. At Stage III, extensive necrosis with destruction progressing beyond the alveolar region, surgical debridement or resection is required, combined with appropriate antibiotic therapy (Ruggiero et al., 2022; Seluki et al., 2023). A recent systematic review demonstrated that while conservative management may prevent disease progression in patients ineligible for surgery, complete resolution of osteonecrosis should not be expected from non-surgical approaches alone (Seluki et al., 2023). Prevention remains the cornerstone strategy: a comprehensive dental assessment with elimination of all infectious dental foci must be performed before initiating any bisphosphonate therapy, particularly by the intravenous route (Ruggiero et al., 2022; Kawahara et al., 2021; McGowan et al., 2018).

Regarding discontinuation of antiresorptive agents, commonly referred to as a drug holiday, available evidence remains insufficient to justify systematic interruption of these treatments, particularly in patients with malignant disease or severe immunosuppression, in whom the risk of tumor-induced hypercalcemia or skeletal-related event relapse must be carefully weighed against the uncertain benefit on BRONJ evolution (Ruggiero et al., 2022; Seluki et al., 2023). Furthermore, the prolonged half-life of bisphosphonates in bone tissue, exceeding ten years for nitrogen-containing derivatives, renders any rapid pharmacological decontamination through simple treatment interruption largely ineffective (AlRowis et al., 2022).

4. CONCLUSION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) represents a severe and potentially life-threatening iatrogenic complication of antiresorptive therapy, whose clinical significance is amplified in oncological patients receiving high-dose intravenous bisphosphonates. The present case of a 29-year-old woman with acute myeloid leukemia illustrates the devastating potential of BRONJ in young immunocompromised patients, characterized by a fulminant clinical course with extensive maxillary sequestration, recurrent infectious episodes, and a fatal outcome within weeks of diagnosis. This observation underscores several critical points that warrant emphasis.

First, the combination of intravenous bisphosphonate therapy and intensive chemotherapy-induced immunosuppression creates a particularly hostile biological environment, dramatically lowering the threshold for osteonecrosis development and accelerating disease progression beyond the patterns typically described in osteoporotic patients on oral regimens. Second, the exclusive involvement of the maxilla, a less frequently affected site compared to the mandible, with complete dentoalveolar sequestration extending from tooth 13 to tooth 25, reflects the severity of bone turnover suppression achievable even within a short exposure window when pharmacological potency is high. Third, the radiological contribution of CBCT proved decisive in this case, enabling precise three-dimensional delineation of the sequestrated block and guiding clinical staging, in a manner unachievable by conventional panoramic radiography alone. From a preventive standpoint, this case reinforces the absolute necessity of systematic pre-therapeutic oral assessment prior to initiating any intravenous bisphosphonate regimen, with early elimination of all potential infectious dental foci. Close interdisciplinary collaboration between oncologists, hematologists, oral and maxillofacial surgeons, and dental practitioners is not optional but essential, particularly in young cancer patients whose immunological vulnerability exponentially compounds the inherent risk of BRONJ. Despite recent progress in understanding its pathophysiology and in refining staging and treatment protocols, BRONJ remains a condition for which prevention is immeasurably more effective than cure, and for which no universally accepted therapeutic standard has yet been established (Ruggiero et al., 2022; Seluki et al., 2023).

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